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(54) Title: COMBINATION OF AN ADENOSINE A_{2A}-RECEPTOR AGONIST AND TIOTROPIUM OR A DERIVATIVE THEREOF FOR TREATING OBSTRUCTIVE AIRWAYS AND OTHER INFLAMMATORY DISEASES

(57) Abstract: A combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (i) an adenosine A_{2A} receptor agonist; and (ii) an anti-cholinergic agent, preferably comprising a member selected from the group consisting of tiotropium and derivatives thereof; the combination being therapeutically effective in the treatment of the diseases when administered by inhalation; as well as to a method of treating the obstructive airways and other inflammatory diseases comprising administering separately, simultaneously or sequentially to the mammal by inhalation a therapeutically effective amount of the combination of therapeutic agents; as well as to a pharmaceutical composition comprising a pharmaceutically acceptable carrier together with the combination of therapeutic agents; as well as to a product containing the compounds of the combination for separate, simultaneous or sequential administration by inhalation to a mammal for the treatment of obstructive airways and other inflammatory diseases. It is preferred that the anti-cholinergic agent component be tiotropium bromide.

COMBINATION OF AN ADENOSINE A_{2A}-RECEPTOR AGONIST AND TIOTROPIUM OR A DERIVATIVE THEREOF FOR TREATING OBSTRUCTIVE AIRWAYS AND OTHER INFLAMMATORY DISEASES

The present invention relates to a combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising an adenosine A_{2A} receptor agonist inhibitor that is therapeutically effective in the treatment of said diseases when administered by inhalation; together with an anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective in the treatment of said diseases when administered by inhalation.

The present invention further relates to a method of treating said obstructive airways and other inflammatory diseases comprising administering to said mammal by inhalation a therapeutically effective amount of said combination of therapeutic agents; and a pharmaceutical composition comprising a pharmaceutically acceptable carrier together with said combination of therapeutic agents; and a package containing a pharmaceutical composition for insertion into a device capable of simultaneous or sequential delivery of said pharmaceutical composition in the form of an aerosol or dry powder dispersion to said mammal, where said device is a metered dose inhaler or a dry powder inhaler. It is preferred that said anti-cholinergic agent component be tiotropium bromide

Background of the Invention

The present invention is concerned with novel combinations an adenosine A_{2A} receptor agonist and tiotropium, or a derivative thereof, that are useful in the treatment of obstructive airways and other inflammatory diseases. Of particular importance as an object of these treatment combinations are the obstructive airways diseases asthma, chronic obstructive pulmonary disease (COPD), and other obstructive airways diseases exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm, especially COPD.

In particular, the combinations of compounds of the present invention are useful in the treatment of respiratory diseases and conditions comprising: asthma, acute respiratory distress syndrome,

chronic pulmonary inflammatory disease, bronchitis, chronic bronchitis, chronic obstructive pulmonary (airway) disease, and silicosis; or immune diseases and conditions comprising: allergic rhinitis and chronic sinusitis.

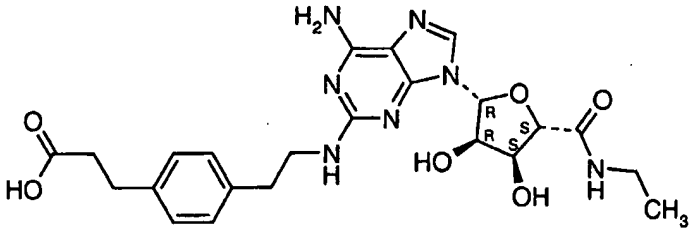
The novel combinations of therapeutic agents with which the present invention is concerned and which are used for the treatment of obstructive airways and other inflammatory diseases, especially asthma, COPD, and other obstructive airways diseases exacerbated by bronchial hyper-reactivity and bronchospasm, comprise the following: an adenosine A_{2A} receptor agonist that includes alentemol, apomorphine, bromocriptine, cabergoline, fenoldopam, lisuride, naxagolide, pergolide, levodopa, pramipexole, quinpirole, ropinirole, or talipexole; together with an anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof, especially tiotropium bromide.

Adenosine A_{2A} Receptor Agonists

The class of adenosine A_{2A} receptor agonists useful in the novel combinations of therapeutic agents of the present invention comprise compounds which exhibit an acceptably high affinity for the A_{2A}-subtype of adenosine receptor and acceptably high therapeutic index for lung effects compared with effects in the periphery after inhalation. Adenosine has a wide range of physiologic activities, including immune and inflammatory responses, which are receptor-mediated and involve interaction with at least four types of plasma membrane receptors. These receptors are commonly referred to as A_1, A_{2A}, A_{2B}, and A_3. Synthetic agonist analogs of adenosine have been prepared in the past in order to overcome such problems as the extremely short half-life of adenosine *in vivo*. Adenosine and its analogs have been found to possess a broad spectrum of anti-inflammatory activity that involves a significant variety of immune and inflammatory cells, including neutrophils and eosinophils. Activation of the A_{2A} receptors on neutrophils results in the suppression of the production of reactive oxidants and other mediators of inflammation such as elastase by these cells, as well as decreased expression of β_2-integrins.

A_{2A} receptors are known to exist on lymphocytes, neutrophils, eosinophils, basophils, monocytes/macrophages, epithelial cells, and on the vascular endothelial tissue with which

they interact. Adenosine binding to A_{2A} receptors can decrease inflammation by influencing the activities of a number of these cells types. For example, A_{2A} receptor agonists markedly inhibit oxidative species elicited by physiologic stimulants such as neutrophil chemoattractants, cytokines, and lipid products. The synthetic selective A_{2A} adenosine receptor agonist CGS 21680 inhibits neutrophil superoxidase release. See Visser *et al.*, "Apparent Involvement of the A_{2A} Subtype Adenosine Receptor in the Anti-inflammatory Interactions of CGS 21680, Cyclopentyladenosine, and IB-MECA with Human Neutrophils," *Biochem. Pharmacol.*, **60** 993-999, 2000. CGS 21680 may be represented by Formula (0.2.1):



CGS 21680

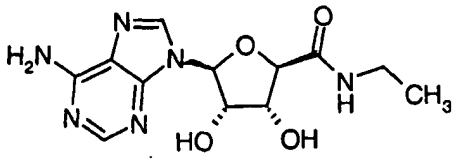
(0.2.1)

Occupancy of adenosine A_{2A} receptors stimulates neutrophil adenylyl cyclase, which results in an increase in intracellular cyclic AMP. In turn, increased neutrophil cyclic AMP results in depression of stimulated-neutrophil oxidative activity. Through a related action on a variety of other inflammatory cell types, the anti-inflammatory properties of A_{2A} agonists extends beyond inhibitory activities on neutrophils. Adenosine also decreases endotoxin-stimulated monocyte/macrophage TNFα release, and it has been observed that endogenous adenosine as well as adenosine analogs reduce human monocyte TNFα production by binding to adenosine A_{2A} receptors. CGS 21680 decreases endotoxin-stimulated adherent human monocyte TNFα production, and in particular human peripheral blood monocyte TNFα production.

Endotoxin-stimulated release of interleukin-6 (IL-6) and interleukin-8 (IL-8) are decreased by adenosine analogs with an order of potency that suggests A_{2A} adenosine receptor activity. Interleukin-10 (IL-10) has anti-inflammatory activity as a result of its ability to decrease endotoxin-stimulated TNFα release from monocytes, to inhibit oxidative activity, and to lower the expression of leukocyte adhesion molecules. Adenosine enhances stimulated human

monocyte production of IL-10; consequently, the binding of adenosine at A_{2A} receptors promotes resolution of any on-going inflammatory response that may be involved.

Activated eosinophils transmigrate into tissues and cause cellular damage and inflammation in such diseases as allergic and non-allergic asthma, allergic rhinitis, and atopic dermatitis. NECA inhibits zymosan-stimulated oxidative activity in guinea pig eosinophils suggesting an A_{2A} mediated process. Thus, adenosine and adenosine A_{2A} receptor agonist analogs, by binding to A_{2A} receptors on eosinophils, inhibit stimulated release of reactive oxygen species, a response which parallels the inhibitory effect of A_{2A} receptors on neutrophils. NECA may be represented by Formula (0.2.2):

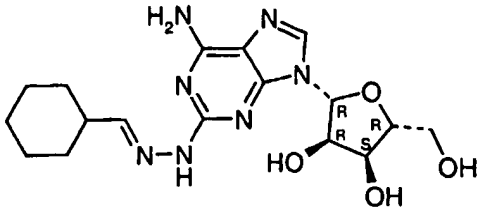


NECA

(0.2.2)

Further, inhaled adenosine A_{2A} receptor agonists inhibit the recruitment of eosinophils into lungs of sensitized guinea-pigs via action in the lungs (see WO 99/67263). This is important as adenosine A_{2A} receptor agonists relax blood vessels and lower blood pressure in animals thus the anti-inflammatory action of adenosine A_{2A} receptor agonists is ideally produced by an inhaled agent which has a high therapeutic index for activity in the lung compared with the peripheral compartment.

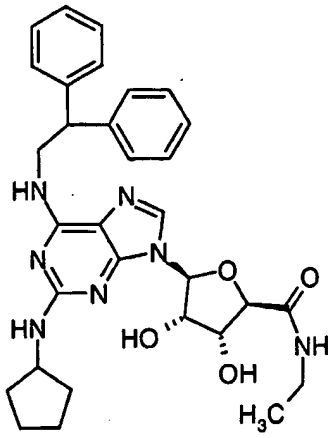
It is known that the selective adenosine A_{2A} receptor agonist, 2-cyclohexyl-methylidene-hydrazino-adenosine (WRC-0470) decreases the inflammatory response in two *in vivo* models of inflammation. See Martin *et al.*, "Pharmacology of 2-Cyclohexyl-methylidene-hydrazino-adenosine (WRC-0470), a Novel, Short-Acting Adenosine A_{2A} Receptor Agonist That Produces Selective Coronary Vasodilation," *Drug Dev. Res.*" **40** 313-324, 1997. WRC-0470 may be represented by Formula (0.2.3):



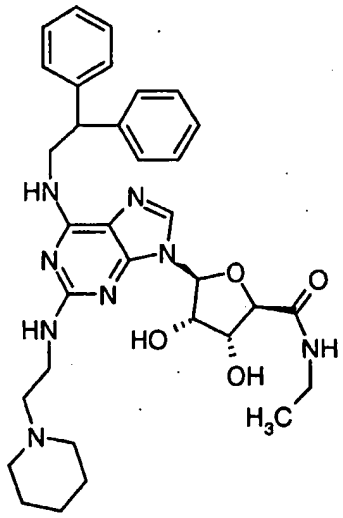
WRC-0470

(0.2.3)

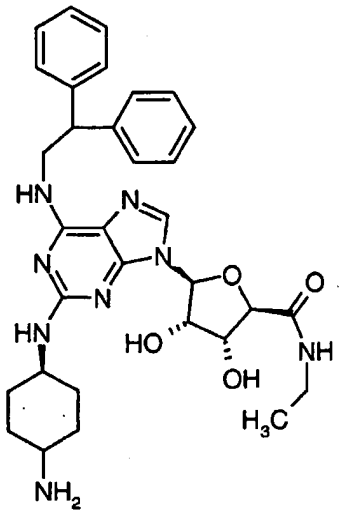
Adenosine A_{2A} receptor agonist analogs have been prepared in the past and their structure-activity relationships have been studied using binding assays of various types. In one such study it has been found that compounds with both a lipophilic N6-substituent and an amino-functionalized 2-position substituent are highly active at the A_{2A} receptor on the human neutrophil. Further, analogs have been discovered that possess significantly improved aqueous solubility while still retaining activity at the A_{2A} receptor on the human neutrophil on the order of at least 10 times that of NECA. See Keeling *et al.*, "The Discovery and Synthesis of Highly Potent, A_{2A} Receptor Agonists," *Bioorg. Med. Chem. Lett.* **10** 403-406, 2000. Four of the analogs described by Keeling *et al.* may be represented by Formulas (0.2.4), (0.2.5), (0.2.6), and (0.2.7):



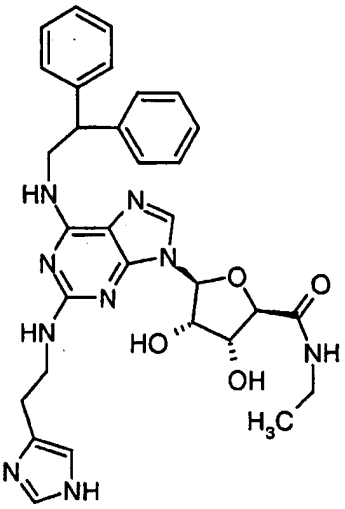
(0.2.4)



(0.2.5)



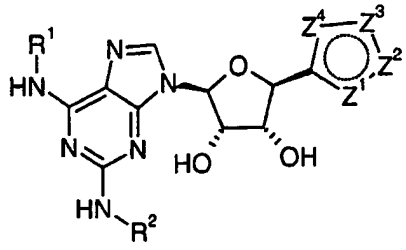
(0.2.6)



(0.2.7)

WO 99/34804 (Linden *et al.*) assigned to The Univ. of Virginia Patent Foundation and published on July 15, 1999, discloses the combination of a PDE4 inhibitor that is preferably rolipram or a rolipram derivative, together with an adenosine A_{2A} receptor agonist to treat an inflammatory disease, especially to reduce restenosis following balloon angioplasty or in conjunction with a gene delivery modality. The A_{2A} agonist component is described as including WRC-0470 and related compounds.

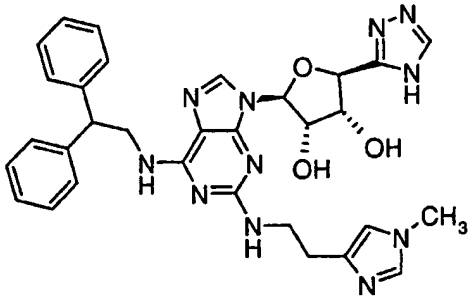
WO 99/67263 (Allen *et al.*) assigned to Glaxo Group Ltd. and published on December 29, 1999 discloses anti-inflammatory adenosine A_{2A} receptor agonists which inhibit leukocyte recruitment and activation, making them useful in providing protection from leukocyte-induced tissue damage. The A_{2A} agonists disclosed may be represented by Formula (0.2.8):



(0.2.8)

wherein R^1 and R^2 are -H; (C_1-C_8) alkyl; (C_3-C_8) cycloalkyl substituted by 0 to 3 groups -$(CH_2)_pR^6$; $H_2NC(=NH)NH(C_1$-$C_6)$ alkyl-; (C_3-C_8) cycloalkyl(C_1-C_6) alkyl-; aryl(C_1-C_6) alkyl-; $aryl_2CHCH_2$-; $R^4R^5N(C_1$-$C_6)$ alkyl- where R^4 and R^5 are -H, (C_1-C_6) alkyl, aryl, aryl(C_1-C_6) alkyl, or NR^4R^5 together are pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl, or N-(C_1-C_6) alkyl-piperazinyl; (C_1-C_6) alkyl-$CH(CH_2OH)$-; aryl(C_1-C_5) alkyl-$CH(CH_2OH)$-; aryl(C_1-C_5) alkyl-$C(CH_2OH)_2$-; a 3- to 7-membered heterocyclyl group; -(C_1-C_6) alkyl-OH; -(C_1-C_6) haloalkyl; pyrrolidinone or piperidinone with N-substituent R^7; aryl; -$(CH_2)_fSO_2NH_g(C_1$-C_4 alkyl-$)_{2-g}$; or -$(CH_2)_fSO_2NH_g$(aryl C_1-C_4 alkyl-$)_{2-g}$; and Z^1, Z^2, Z^3, and Z^4 together with the carbon atom form a 5-membered heterocyclic aromatic ring. It is further disclosed that the adenosine A_{2A} receptor agonists may be used in combination with other therapeutic such as corticosteroids, *e.g.*, fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide, or budesonide; NTHEs, *e.g.*, sodium cromoglycate; β-adrenergic agents, *e.g.*, salmeterol, salbutamol, formoterol, fenoterol, or terbutaline; and anti-infective agents, *e.g.*, antibacterials or antivirals.

A preferred adenosine A_{2A} receptor agonist agent is represented by Formula (0.2.9):



(0.2.9)

For further details concerning adenosine A_{2A} receptor agonists and their use in treating inflammation, see Kull *et al.*, "Differences in the Order of Potency for Agonist But Not Antagonists at Human and Rat Adenosine A_{2A} Receptors," *Biochem. Pharmacol.* **57** 65-75, 1999; and Sullivan and Linden, "Role of A_{2A} Adenosine Receptors in Inflammation," *Drug. Dev. Res.* **45** 103-112, 1998.

Nothing in the above-described state of the art discloses or would suggest to the artisan the novel combinations of therapeutic agents of the present invention comprising an adenosine A_{2A}

receptor agonist together with an anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof.

Muscarinic Receptor Antagonists (Anti-Cholinergic Agents)

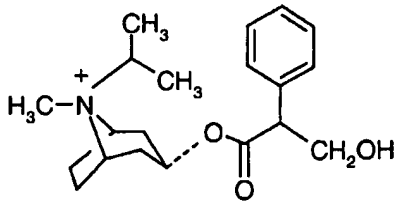
Muscarinic receptor antagonists prevent the passage of, or effects resulting from passage of impulses through the parasympathetic nerves. This action results from their ability to inhibit the action of the neurotransmitter acetylcholine by blocking its binding to muscarinic cholinergic receptors. There are at least three types of muscarinic receptor subtypes. M_1 receptors are found primarily in brain and other tissue of the central nervous system, M_2 receptors are found in heart and other cardiovascular tissue, and M_3 receptors are found in smooth muscle and glandular tissues. The muscarinic receptors are located at neuroeffector sites on, *e.g.*, smooth muscle, and, in particular, M_3-muscarinic receptors are located in airway smooth muscle. Consequently, muscarinic receptor antagonists may also be referred to as anti-cholinergic agents. Atropine and scopolamine are the best known members of this class of therapeutic agents.

The parasympathetic nervous system plays a major role in regulating bronchomotor tone, and bronchoconstriction is largely the result of reflex increases in parasympathetic activity caused in turn by a diverse set of stimuli. Anti-cholinergic agents have a long history of use in the treatment of chronic airway diseases characterized by partially reversible airway narrowing such as COPD and asthma and were used as bronchodilators before the advent of epinephrine. They were thereafter supplanted by β-adrenergic agents and methylxanthines. However, the more recent introduction of ipratropium bromide has led to a revival in the use of anti-cholinergic therapy in the treatment of respiratory diseases. However, there are muscarinic receptors on peripheral organ systems such as salivary glands and gut and therefore systemically active muscarinic receptor antagonists are limited by dry mouth and constipation. Thus the bronchodilatory and other beneficial actions of muscarinic receptor antagonists is ideally produced by an inhaled agent which has a high therapeutic index for activity in the lung compared with the peripheral compartment.

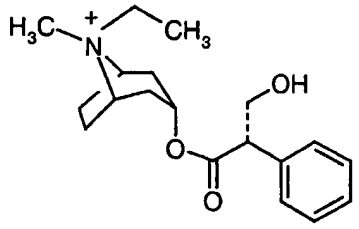
Anti-cholinergic agents also partially antagonize bronchoconstriction induced by histamine, bradykinin, or prostaglandin $F_{2\alpha}$, which is deemed to reflect the participation of parasympathetic efferents in the bronchial reflexes elicited by these agents.

The anti-cholinergic agents tiotropium, ipratropium, and oxitropium are quaternary ammonium compounds in structure, and central effects from these agents are generally lacking because these agents do not readily cross the blood-brain barrier. When these agents are inhaled, their actions are confined almost entirely to the mouth and airways. Even when inhaled at several times the recommended dose, these agents produced little or no change in heart rate, blood pressure, bladder function, intraocular pressure, or pupillary diameter. This selectivity results from the very inefficient absorption of these agents from the lung or gastrointestinal tract. The preclinical and clinical profile of tiotropium is entirely in accord with these characteristics, with the profound difference that tiotropium has a prolonged duration of action resulting from its slow dissociation from the muscarinic M_3 receptor.

Ipratropium and oxitropium may be represented by Formulas (1.0.1) and (1.0.2), respectively:



(1.0.1)

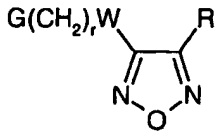


(1.0.2)

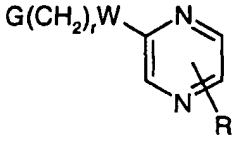
Anti-cholinergic agents having bronchodilator activity known in the art include ambutonium bromide; apoatropine; benzilonium bromide; benztropine mesylate; bevonium methylsulfate; butropium bromide; *N*-butylscopolammonium bromide; cimetropium bromide; clidinium bromide; cyclonium iodide; difemerine; diponium bromide; emepronium bromide; etomidoline; fenpiverinium bromide; fentonium bromide; flutropium bromide; heteronium bromide; hexocyclium methylsulfate; octamylamine; oxyphenonium bromide; pentapiperide; piperilate; poldine methylsulfate; prifinium bromide; propyromazine; sultroponium; tematropium methylsulfate; tiemonium iodide; tiquizium bromide; trimebutine; tropenzile; trospium chloride; and xenytropium bromide.

Adenosine A_{2A} receptor agonists are disclosed and described in detail in the published applications and issued patents set out in the paragraphs that follow.

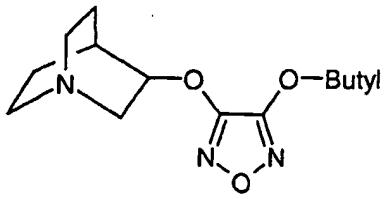
U.S. Patent Nos. 5,605,908 and 5,998,404 assigned to Eli Lilly and Company discloses azacycloalkoxy-substituted pyrazines, oxadiazoles, and related compounds as muscarinic and nicotinic cholinergic agents useful as stimulants of cognitive function and the treatment of Alzheimer's disease, wherein the compounds are of Formulas (1.0.3) and (1.0.4), including a species compound of Formula (1.0.5):



(1.0.3)



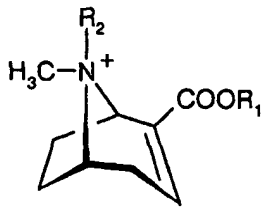
(1.0.4)



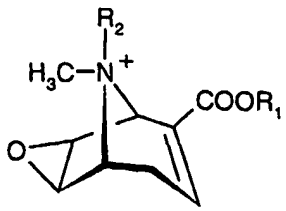
(1.0.5)

wherein W is O or S; R is H; amino; halo; R^4, OR^4, SR^4, SOR^4, or SO_2R^4 where R^4 is optionally substituted alkyl, alkenyl, or alkynyl; cycloalkyl; optionally substituted phenyl; phenyl-CH_2-O(=O)C-; G is optionally substituted alkyl, cycloalkyl, azetidinyl, pyrrolidinyl, piperidinyl, azabicyclo[2.2.2]octyl; and r is 0 to 2.

U.S. Patent No. 5,821,249 assigned to the University of Rochester discloses methylecgonidine and anti-cholinergically active derivatives or analogs thereof that are useful in the prevention or treatment of a disease or disorder treatable by antimuscarinic anti-cholinergic agent, an anti-histaminic agent or a spasmolytic agent, in particular bronchoconstriction in a number of pulmonary diseases such as asthma. The above-mentioned methylecgonidine and its derivatives and epoxide analogs may be represented by Formulas (1.0.6) and (1.0.7), respectively:



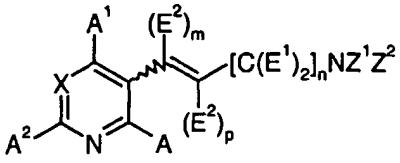
(1.0.6)



(1.0.7)

wherein R_2 is -H, (C_1-C_{10}) alkyl, or an amidine; and R_1 is (C_1-C_{10}) alkyl, or an aryl substituted (C_1-C_{10}) alkyl.

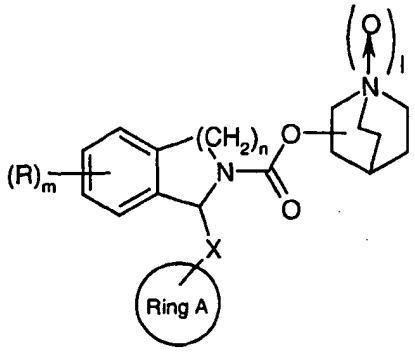
U.S. Patent No. 5,861,423 assigned to R.J. Reynolds Tobacco Co. discloses pyridinylbutenylamine nicotinic cholinertic agents comprising a compound of Formula (1.0.8):



(1.0.8)

wherein X is CR', COR', or CCH_2OR' where R' is H, alkyl, or an optionally substituted aromatic group-containing moiety; E^1 is H, alkyl, or haloalkyl; E^2 is alkyl, or haloalkyl; Z^1 and Z^2 are H, alkyl, or aryl; Z^1Z^2N is heterocyclyl; A, A^1, and A^2 are H, alkyl, or halo; m is 0 or 1; n is 1 to 8; and p is 0 or 1.

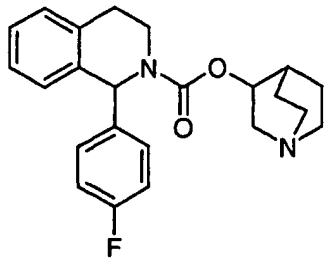
U.S. Patent No. 6,017,927 assigned to Yamanouchi Pharmaceutical Co. discloses quinuclidine derivatives that have a selective antagonistic effect on muscarinic M_3 receptors and are useful as a preventive treatment or remedy for urologic diseases, respiratory diseases, or digestive diseases. The above-mentioned derivatives may be represented by Formula (1.0.9):



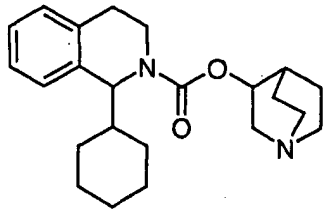
(1.0.9)

wherein Ring A is aryl, cycloalkyl, cycloalkenyl, heteroaryl of 1-4 heteroatoms N, O, or S, or optionally substituted 5-7-membered saturated heterocyclic; X is a single bond or methylene; R is halo, hydroxy, lower alkoxy, carboxyl, lower alkoxycarbonyl, lower acyl, mercapto, lower alkylthio, sulfonyl, lower alkylsulfonyl, sulfinyl, lower alkylsulfinyl, sulfonamido, lower

alkylsulfonamido, carbamoyl, thiocarbamoyl, mono- or di-lower alkylcarbamoyl, nitro, cyano, amino, mono- or di-lower alkylamino, methylenedioxy, ethylenedioxy, or lower alkyl optionally substituted by halo, hydroxy, lower alkoxy, amino, or mono- or di-lower alkylamino; l is 0 or 1; m is 0 or 1-3; and n is 1 or 2. Preferred compounds of the type described include, *e.g.*, those represented by Formulas (1.0.10) and (1.0.11):

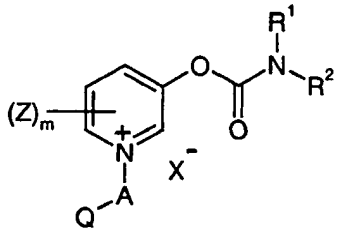


(1.0.10)

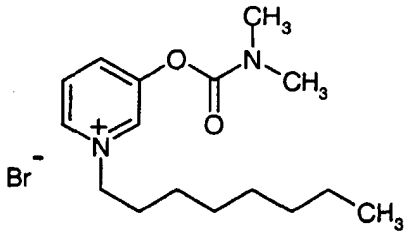


(1.0.11)

WO 97/08146 (Rachaman *et al.*) discloses carbamate derivatives of pyridostigmine useful in the treatment of cognitive impairments associated with cholinergic perturbances such as Alzheimer's disease comprising a compound of Formula (1.0.12), including a species compound of Formula (1.0.13):



(1.0.12)

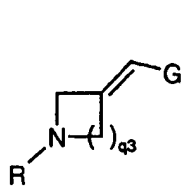


(1.0.13)

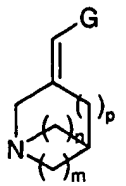
wherein R^1 is H, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl; R^2 is H, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl; A is alk(en/yn)ylene; Z is dialkylcarbamoyl or alkyl; m is 0 or 1; Q is a transporter recognition moiety for biological membranes, optionally coupled to a physiologically active acceptable moiety; and X is an anion.

WO 97/11072 assigned to Novo Nordisk A/S discloses azacyclic and azabicyclic nicotinic cholinergic agents useful in the treatment of Alzheimer's disease, Parkinson's disease, obesity,

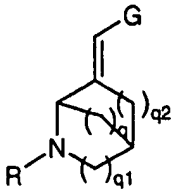
severe pain, tobacco withdrawal, and anxiety comprising a compound of Formula (1.0.14); (1.0.15); or (1.0.16); including a species compound of Formula (1.0.17):



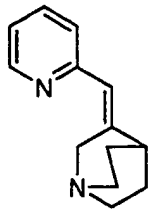
(1.0.14)



(1.0.15)



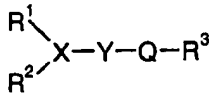
(1.0.16)



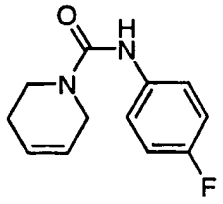
(1.0.17)

wherein m and n are 1 to 3; p, q, q1, and q2 are 0 to 2; q3 is 1 to 5; R is H, or alkyl; and G is selected from optionally substituted, 6-membered, N-heterocycles containing 1 to 4 N atoms.

WO 00/51970 assigned to Fujisawa Pharmaceutical Co., Ltd. discloses aryl and heteroaryl amide potentiators of cholinergic activity useful as anti-amnesia or anti-dementia agents comprising a compound of Formula (1.0.18), including a species compound of Formula (1.0.19):



(1.0.18)



(1.0.19)

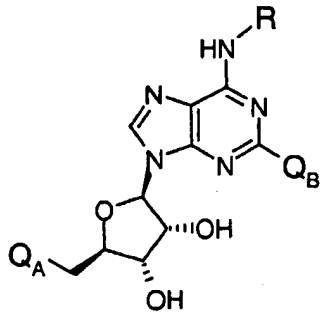
wherein R^1 and R^2 are aryl or ar(lower)alkyl, or together form lower alkylene, each of which is optionally substituted with aryl or condensed with a cyclic hydrocarbon optionally substituted by lower alkyl, lower alkoxy, aryl, arylamino, or aryloxy, each of which is optionally substituted by lower alkoxy or halogen, pyridyl, or pyridylamino; X is CH or N; Y is a single bond or -NH-; and Q is -C(=O)-.

Summary of the Invention

The present invention is concerned with novel combinations of therapeutic agents which are useful in the treatment of obstructive airways and other inflammatory diseases, especially asthma, COPD, and other obstructive airways diseases exacerbated by bronchial hyper-reactivity and bronchospasm. The novel combinations comprise the following: (i) an adenosine A_{2A} receptor agonist; together with (ii) an anti-cholinergic agent, preferably comprising a member selected from the group consisting of tiotropium and derivatives thereof, the combination being therapeutically effective in the treatment of the diseases when administered by inhalation.

The advantage of the present combination is to provide optimal control of airway caliber through the mechanism most appropriate to the disease pathology, namely muscarinic receptor antagonism, together with effective suppression of inappropriate inflammation. By combining both antimuscarinic and adenosine A_{2A} receptor agonists via the inhaled route, the benefits of each class are realized without the unwanted peripheral effects. Further, the combination results in unexpected synergy, producing greater efficacy than maximally tolerated doses of either class of agent used alone acting as they do on distinct disease processes important to the signs and symptoms suffered by the patients.

The present invention is further concerned with the above-recited combination of therapeutic agents wherein the adenosine A_{2A} receptor agonist is a compound of Formula (3.0.1), or a pharmaceutically acceptable salt of the compound, recited in the paragraphs immediately below.



(3.0.1)

wherein:

$-Q_A$ is $-OR^1$; $-C(=O)NHR^3$; $-R^5$; or $-R^7$;

— wherein —

R^1 is -H; (C_1-C_4) alkyl; or cyclopropylmethyl;

R^3 is -H; (C_1-C_6) alkyl; (C_3-C_7) cycloalkyl; cyclopropylmethyl; phenyl; naphthyl, azetidin-3-yl; pyrrolidin-3-yl; piperidin-3-yl; piperidin-4-yl; or HET; where the azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl are substituted by 0 or 1 of (C_1-C_6) alkyl; and

— where —

HET is C-linked pyrrolyl; imidazolyl; triazolyl; thienyl; furyl; thiazolyl; oxazolyl; thiadiazolyl; oxadiazolyl; pyridinyl; pyrimidinyl; pyridazinyl; pyrazinyl; indolyl; isoindolyl; quinolinyl; isoquinolinyl; benzimidazolyl; quinazolinyl; phthalazinyl; benzoxazolyl; or quinoxalinyl; each substituted by 0-3 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or halo;

R^5 is $-CH_2OH$; or $-C(=O)NR^{14}R^{16}$;

where R^{14} and R^{16} are each independently -H; or (C_1-C_6) alkyl substituted by 0 or 1 of cyclopropyl;

R^7 is a C-linked, 5-membered aromatic heterocycle containing (a) 1-4 ring nitrogen atoms, or (b) 1-2 ring nitrogen atoms and 1 oxygen or 1 sulfur ring atom, where the heterocycle is substituted by 0 or 1 (C_1-C_6) alkyl substituted by 0 or 1 of phenyl, -OH, (C_1-C_6) alkoxy, or $-NR^{18}R^{20}$, where

R^{18} and R^{20} are each independently -H; (C_1-C_6) alkyl; or taken together with the nitrogen atom to which they are attached, are azetidinyl, pyrrolidinyl, or piperidinyl, each substituted by 0 or 1 of (C_1-C_6) alkyl;

and

$-Q_B$ is $-(CH_2)_n-A-R^9$; $-C(=O)N(R^{11})-B-R^{13}$; $-CH_2-NHS(=O)_2-B-R^{15}$; or $-L-D-N(R^{17})-E-NR^{19}R^{21}$;

wherein

n is 1 or 2;

A is $-NR^{22}-$; $-NR^{22}C(=O)-$; $-NR^{22}C(=O)NR^{24}-$; $-NR^{22}C(=O)O-$; $-OC(=O)NR^{22}-$; $-C(=O)NR^{22}-$; $-NR^{22}S(=O)_2-$; $-S(=O)_2NR^{22}-$; -O-; -S-; or $-S(=O)_2-$;

— where —

R^{22} and R^{24} are each independently -H; (C_1-C_4) alkyl; or benzyl substituted by 0-3 of (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo, or cyano;

R^9 is a group of the formula -$(CH_2)_p$-R^{26}-W;

— where —

p is 0, 1, or 2;

R^{26} is a bond; (C_1-C_4) alkylene; (C_3-C_7) cycloalkylene; phenylene; or naphthylene; the cycloalkylene, phenylene and naphthylene each being substituted by 0-3 of (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo, or (C_1-C_4) alkoxy(C_1-C_4) alkylene;

W is a member selected from the group consisting of:

(a) -H; -$NR^{28}R^{30}$; $R^{28}R^{30}$N-alkylene-; -OR^{28}; -C(=O)OR^{28}; -OC(=O)R^{28}; -$S(=O)_2R^{28}$; -CN; -$S(=O)_2NR^{28}R^{30}$; -$NR^{28}C(=O)R^{30}$; -$NR^{28}S(=O)_2R^{30}$; or -C(=O)$NR^{28}R^{30}$;

— where —

R^{28} and R^{30} are the same or different and are selected from the group consisting of -H, (C_1-C_4) alkyl, phenyl and benzyl;

— provided that —

(i) when W is -OC(=O)R^{28}, -$S(=O)_2R^{28}$, -$NR^{28}C(=O)R^{30}$, or -$NR^{28}S(=O)_2R^{30}$, then the terminal R^{30} is not -H; and,

(ii) R^{26} is a bond, p is 0, and W is -H only when A is -NR^{22}, -$NR^{22}C(=O)NR^{24}$, -$OC(=O)NR^{22}$, -$C(=O)NR^{22}$, -$S(=O)_2NR^{22}$, -O-, or -S-;

(b) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R^{26} by a ring carbon atom;

— and —

(c) N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each substituted by 0-3 (C_1-C_4) alkyl; with the proviso that -$(CH_2)_p$-R^{26}- is not -CH_2-; and

where:

A is -NR^{22}-, -C(=O)NR^{22}-, -OC(=O)NR^{22}-, or -$S(=O)_2NR^{22}$-; R^{22} and R^9 may be taken together with the nitrogen atom to which they are attached to form an azetidine, pyrrolidine, piperidine or piperazine ring, substituted by 0-3 of (C_1-C_4) alkyl;

R^{11} is -H; or (C_1-C_6) alkyl;

B is a bond; or (C_1-C_6) alkylene; and

R^{13} is a member selected from the group consisting of:

(a) -H; (C_1-C_6) alkyl; -C(=O)OR^{32}; -CN; -C(=O)$NR^{32}R^{34}$; -(C_3-C_8) cycloalkyl; phenyl; or naphthyl, where the -(C_3-C_8) cycloalkyl, phenyl, or naphthyl is substituted by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_1-C_6)alkyl, $R^{32}R^{34}N$(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, fluoro(C_1-C_6)alkoxy, (C_2-C_5) alkanoyl, halo, -OR^{32}, cyano, -C(=O)OR^{32}, (C_3-C_8) cycloalkyl, -$S(=O)_mR^{35}$ where m is 0, 1, or 2, -$NR^{32}R^{34}$, -$S(=O)_2NR^{32}R^{34}$, -C(=O)$NR^{32}R^{34}$, -$NR^{32}C(=O)R^{35}$, or -$NR^{32}S(=O)_2R^{35}$; with the proviso that R^{13} is not -H when B is a bond;

(b) -$NR^{32}R^{34}$; -OR^{32}; -C(=O)OR^{32}; -OC(=O)R^{34}; -$S(=O)_2R^{34}$; -CN; -$S(=O)_2NR^{32}R^{34}$; -$NR^{32}COR^{34}$; or -C(=O)$NR^{32}R^{34}$; when B is (C_2-C_6) alkylene;

(c) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle having either from 1 to 4 ring nitrogen atom(s), or 1 or 2 nitrogen and 1 oxygen or 1 sulfur ring atoms;

C-substituted by 0-2 of oxo, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $R^{36}R^{38}N$(C_1-C_6) alkyl, halo(C_1-C_6) alkyl, fluoro(C_1-C_6) alkoxy, fluoro(C_2-C_5) alkanoyl, halo, cyano, -OR^{36}, -R^{37}, -C(=O)R^{36}, -$NR^{36}R^{38}$, -C(=O)OR^{36}, -$S(=O)_mR^{37}$ where m is 0, 1, or 2, -$S(=O)_2NR^{36}R^{38}$, -C(=O)$NR^{36}R^{38}$, -$NR^{36}S(=O)_2R^{37}$, or -$NR^{36}C(=O)R^{37}$; and

N-substituted by 0-2 of (C_1-C_6) alkoxy(C_1-C_6) alkyl, $R^{36}R^{38}N$(C_2-C_6) alkyl, halo(C_1-C_6) alkyl, fluoro(C_2-C_5) alkanoyl, -R^{37}, -C(=O)R^{36}, -C(=O)OR^{37}, -$S(=O)_2R^{37}$, -$S(=O)_2NR^{36}R^{38}$, or -C(=O)$NR^{36}R^{38}$;

— and —

(d) N-linked azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; homopiperazinyl; or morpholinyl; when B is C_2-C_6 alkylene;

each C-substituted by 0-2 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_1-C_6) alkyl, $R^{32}R^{34}N$(C_1-C_6) alkyl, halo(C_1-C_6) alkyl, fluoro(C_1-C_6) alkoxy, (C_2-C_5) alkanoyl, halo, -OR^{32}, cyano, -C(=O)OR^{32}, (C_3-C_8) cycloalkyl, -$S(=O)_mR^{35}$ where m is 0, 1, or 2, -$NR^{32}R^{34}$, -$S(=O)_2NR^{32}R^{34}$, -C(=O)$NR^{32}R^{34}$, -$NR^{32}C(=O)R^{35}$, or -$NR^{32}S(=O)_2R^{35}$; and

each the piperazinyl or homopiperazinyl N-substituted by 0-2 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_2-C_6) alkyl, $R^{32}R^{34}N$(C_2-C_6) alkyl, fluoro(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, -C(=O)OR^{35}, (C_3-C_8) cycloalkyl, -$S(=O)_2R^{35}$, -$S(=O)_2NR^{32}R^{34}$, or -C(=O)$NR^{32}R^{34}$;

— where —

R^{32} and R^{34} are each independently -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl; or R^{32} and R^{34} are taken together with the nitrogen atom to which they are attached to form azetidinyl; pyrrolidinyl; piperidinyl; morpholinyl; piperazinyl; homopiperidinyl;

homopiperazinyl; or tetrahydroisoquinolinyl; each substituted on a ring carbon atom by 0 or 1 of $(C_1\text{-}C_6)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, phenyl, $(C_1\text{-}C_6)$ alkoxy-$(C_1\text{-}C_6)$ alkyl, $R^{54}R^{56}N$-$(C_1\text{-}C_6)$ alkyl, fluoro-$(C_1\text{-}C_6)$ alkyl, $-C(=O)NR^{54}R^{56}$, $-C(=O)OR^{54}$, or $(C_2\text{-}C_5)$ alkanoyl; further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0 or 11 of fluoro-$(C_1\text{-}C_6)$ alkoxy, halo, $-OR^{54}$, cyano, $-S(=O)_mR^{55}$, $-NR^{54}R^{56}$, $-S(=O)_2NR^{54}R^{56}$, $-NR^{54}C(=O)R^{55}$, or $-NR^{54}S(=O)_2R^{55}$; and the piperazin-1-yl and homopiperazin-1-yl are substituted on the secondary nitrogen atom by 0 or 1 of $(C_1\text{-}C_6)$ alkyl, phenyl, $(C_1\text{-}C_6)$ alkoxy-$(C_2\text{-}C_6)$ alkyl, $R^{54}R^{56}N(C_2\text{-}C_6)$ alkyl, fluoro$(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_5)$ alkanoyl, $-C(=O)OR^{55}$, $(C_3\text{-}C_6)$ cycloalkyl, $-S(=O)_2R^{55}$, $-S(=O)_2NR^{54}R^{56}$, or $-C(=O)NR^{54}R^{56}$;

R^{35} is $(C_1\text{-}C_6)$ alkyl; $(C_3\text{-}C_8)$ cycloalkyl; or phenyl;

R^{36} and R^{38} are each independently -H; $(C_1\text{-}C_6)$ alkyl; $(C_3\text{-}C_8)$ cycloalkyl; phenyl; naphthyl; or HET where HET has the same meaning as defined above;

— and —

R^{37} is $(C_1\text{-}C_6)$ alkyl; $(C_3\text{-}C_8)$ cycloalkyl; phenyl; naphthyl; or HET where HET has the same meaning as defined above;

R^{15} has the same meaning as parts (a), (b), and (c) of R^{13} defined above, including all sub-substituents thereof;

L is a bond or a linking group $-C(=O)NR^{40}$, where R^{40} has the same meaning as R^{11} defined above;

D is $-CH_2-$; $-CH_2CH_2-$; or $-CH_2CH_2CH_2-$; each substituted by 0 or 1 of $(C_1\text{-}C_6)$ alkyl, or $(C_3\text{-}C_8)$ cycloalkyl;

E is $-C(=O)-$; $-C(=S)-$; $-S(=O)_2-$; or $-C[=N(CN)]-$;

R^{17} has the same meaning as R^{11} defined above;

R^{19} is -H; $(C_1\text{-}C_6)$ alkyl; $(C_3\text{-}C_8)$ cycloalkyl; or benzyl;

R^{21} is azetidin-3-yl; pyrrolidin-3-yl; piperidin-3-yl; piperidin-4-yl; homopiperidin-3-yl; or homopiperidin-4-yl; each substituted by 0-2 of $(C_1\text{-}C_6)$ alkyl, $(C_3\text{-}C_8)$ cycloalkyl, or benzyl; or $-(C_2\text{-}C_6)$ alkylene-R^{42}; or $-(C_1\text{-}C_6)$ alkylene-R^{44};

— or —

R^{19} and R^{21} are taken together with the nitrogen atom to which they are attached to form azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; homopiperidinyl; or homopiperazinyl; each substituted on a ring nitrogen or carbon atom by 0-3 of $(C_1\text{-}C_6)$ alkyl, or

(C_3-C_8) cycloalkyl; and further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0-3 of -$NR^{46}R^{48}$;

— where —

R^{42} is $NR^{50}R^{52}$; or azetidin-1-yl; pyrrolidin-1-yl; piperidin-1-yl; morpholin-4-yl; piperazin-1-yl; homopiperidin-1-yl; homopiperazin-1-yl; or tetrahydroisoquinolin-1-yl; each substituted on a ring carbon atom by 0 or 1 (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, phenyl, (C_1-C_6) alkoxy-(C_1-C_6) alkyl, $R^{54}R^{56}N$-(C_1-C_6) alkyl, fluoro-(C_1-C_6) alkyl, -$C(=O)NR^{54}R^{56}$, -$C(=O)OR^{54}$, or (C_2-C_5) alkanoyl; and further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0 or 1 of fluoro(C_1-C_6) alkoxy, halo, -OR^{54}, cyano, -$S(=O)_mR^{55}$, -$NR^{54}R^{56}$, -$S(=O)_2NR^{54}R^{56}$, -$NR^{54}C(=O)R^{55}$, or -$NR^{54}S(=O)_2R^{55}$; and further the piperazin-1-yl and homopiperazin-1-yl are substituted on the ring nitrogen atom not attached to the (C_2-C_6) alkylene group by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy-(C_2-C_6) alkyl, $R^{54}R^{56}N$-(C_2-C_6) alkyl, fluoro-(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, -$C(=O)OR^{55}$, (C_3-C_8) cycloalkyl, -$S(=O)_2R^{55}$, -$S(=O)_2NR^{54}R^{56}$, or -$C(=O)NR^{54}R^{56}$;

R^{44} is phenyl; pyridin-2-yl; pyridin-3-yl; or pyridin-4-yl; each substituted by 0 or 1 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, or cyano;

R^{46} and R^{48} are each independently -H; or (C_1-C_6) alkyl; or, taken together with the nitrogen atom to which they are attached, represent azetidinyl, pyrrolidinyl, or piperidinyl; each substituted by 0 or 1 of (C_1-C_6) alkyl;

R^{50} is -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or benzyl;

R^{52} is -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; phenyl; benzyl; fluoro-(C_1-C_6) alkyl; -$C(=O)NR^{54}R^{56}$; -$C(=O)OR^{55}$; (C_2-C_5) alkanoyl; or -$S(=O)_2NR^{54}R^{56}$;

R^{54} and R^{56} are each independently -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl;

R^{55} is (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl;

-R is -H; (C_1-C_6) alkyl; or fluorenyl; where the (C_1-C_6) alkyl is substituted by 0-2 of phenyl, or naphthyl; where the phenyl or naphthyl is substituted by 0 or 2 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, or cyano;

or a pharmaceutically acceptable salt thereof.

Suitable adenosine A_{2A} receptor agonists for use in the invention include the compounds generally and specifically disclosed in WO 00/23457, WO 00/77018, WO 01/27131 and WO

01/27130, each of which is hereby incorporated by reference in its entirety, and the unpublished applications attached to this application as Annex 1, Annex 2, and Annex 3.

Preferred adenosine A_{2A} receptor agonists for use in the invention include:

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide (Example 15 of WO 00/23457);

cis -(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)amino]-2-{[(4-isopropylcyclohexyl)amino]methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol and *trans*-(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)amino]-2-{[(4-isopropylcyclohexyl)amino]methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol (Example 17 of WO 00/23457);

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide (Example 1 of WO 01/27130);

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(isopropylsulfonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide (Example 3 of WO 01/27131);

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide (Example 1 of WO 00/77018);

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide (Example 1 of Annex 1);

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-(diisopropylamino)ethyl]urea (Example 1 of Annex 2); and

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[1-(2-pyridinyl)-4-piperidinyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide (Example 8 of Annex 3), and the pharmaceutically acceptable salts and solvates thereof.

The present invention is also concerned with novel combinations of therapeutic agents wherein the adenosine A_{2A} receptor agonist is a member selected from the group consisting of the following:

9-[(2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-2-phenylacetamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzenesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-[2-(benzylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-(cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-{[(cyclohexylmethyl)amino]methyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-[(cyclopentylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-1-propanesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-{2-[2-(cyclohexylamino)ethyl]-6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-(2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)benzenesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[2-(isopropylamino)ethyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperdinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-phenylethyl-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(4-isopropyl-1-piperdinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[3-(1-pyrrolidinyl)propyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(4-morpholinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-(2-pyridinylmethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(2-pyridinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-*N*-[2-(dimethylamino)ethyl]-6-[(2,2-diphenylethyl)amino]- 9*H*-purine-2-carboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-(phenylethylamino)-9*H*-purin-2-yl]methyl}benzenesulfonamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purin-2-yl}methyl)benzenesulfonamide;

2-[cyclopentyl(isopropyl)amino]-*N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-ethanesulfonamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[(benzylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(propylsulfonyl)amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(isopropylsulfonyl)amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(phenylsulfonyl)amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[([1,1'-biphenyl]-4-ylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(naphthylsulfonyl)amino]-methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-di-isopropylamino)ethyl]urea;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-(1-piperidinyl)ethyl]urea;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]-methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-{2-{[({[2-(1-piperidinyl)ethyl]-amino}-carbonyl)amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({6-{[2,2-bis(4-chlorophenyl)ethyl]amino}-9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-(2-di-isopropylamino)ethyl]urea;

N-[2-(dicyclobutylamino)ethyl]-N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)urea;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(4-isopropyl-1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

N-{2-[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]ethyl}-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-*N*-{2-[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]ethyl}-6-[(2,2-diphenylethyl)amino] -9*H*-purine-2-carboxamide;

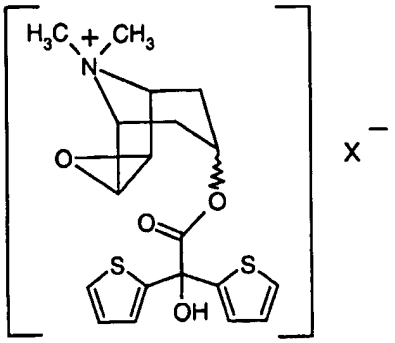
6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(4-isopropyl-1-piperidinyl)ethyl]amino}-carbonyl)-amino]ethyl}-9*H*-purine-2-carboxamide;

N-(2-{[({2-[cyclopentyl(isopropyl)amino]ethyl}amino)carbonyl]amino}ethyl)-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetra-hydro-2-furanyl}-9*H*-purine-2-carboxamide; and

N-(2-{[({2-[cyclohexyl(isopropyl)amino]ethyl}amino)carbonyl]amino}ethyl)-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetra-hydro-2-furanyl}-9*H*-purine-2-carboxamide,

and the pharmaceutically acceptable salts and solvates thereof.

Tiotropium and derivatives thereof is a compound of Formula (1.1.1):

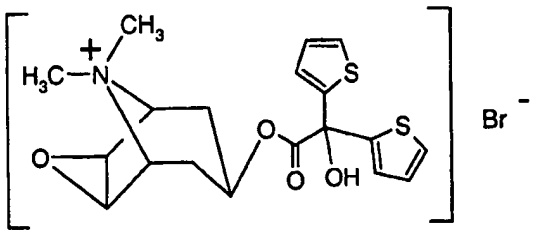


(1.1.1)

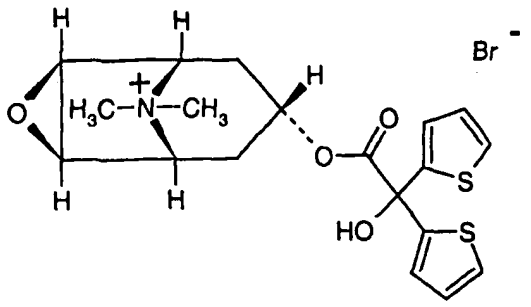
wherein X^- is a physiologically acceptable anion, preferably selected from the group consisting of fluoride, F^-; chloride, Cl^-; bromide, Br^-; iodide, I^-; methanesulfonate, $CH_3S(=O)_2O^-$; ethanesulfonate, $CH_3CH_2S(=O)_2O^-$; methylsulfate, $CH_3OS(=O)_2O^-$; benzene sulfonate, $C_6H_5S(=O)_2O^-$; and *p*-toluenesulfonate, $4\text{-}CH_3\text{-}C_6H_5S(=O)_2O^-$.

The present invention is concerned in particular with the above-recited anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof, wherein the physiologically acceptable anion, X^-, is bromide, Br^-; and further wherein the tiotropium and derivatives thereof are 3-α compounds.

The present invention is further concerned in particular with the above-recited anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof, wherein the member thereof is tiotropium bromide, (1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, represented by Formula (1.1.2) or Formula (1.1.3):



(1.1.2)



(1.1.3)

Of particular importance is tiotropium bromide in the form of its crystalline monohydrate as disclosed in WO 02/30928, which is hereby incorporated by reference in its entirety.

The present invention is also concerned with a method for the treatment of obstructive airways and other inflammatory diseases in a mammal in need of such treatment, comprising administering to the mammal by inhalation a therapeutically effective amount of a combination of therapeutic agents comprising (i) an adenosine A_{2A} receptor agonist; and (ii) an anti-cholinergic agent, preferably comprising a member selected from the group consisting of tiotropium and derivatives thereof, wherein the combination is therapeutically effective in the treatment of the above-mentioned diseases when administered by inhalation.

The present invention is concerned with the above-described method of treatment wherein the obstructive airways or other inflammatory disease comprises asthma, chronic obstructive pulmonary disease (COPD), and other obstructive airways diseases exacerbated by bronchial hyper-reactivity and bronchospasm.

The present invention is further concerned with the above-described methods of treatment wherein the mammal in need of treatment is a human being.

The present invention is still further concerned with the above-described methods of treatment wherein the administration by inhalation comprises simultaneous or sequential delivery of the combination of therapeutic agents of the present invention in the form of an aerosol or dry powder dispersion.

The present invention is concerned with pharmaceutical compositions suitable for administration by inhalation comprising a pharmaceutically acceptable carrier together with a combination of therapeutic agents comprising (i) an adenosine A_{2A} receptor agonist that is therapeutically effective when administered by inhalation; and (ii) an anti-cholinergic agent, preferably comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective when administered by inhalation.

The present invention is further concerned with the above-described pharmaceutical compositions suitable for administration by inhalation comprising a package containing the pharmaceutical compositions for insertion into a device capable of simultaneous or sequential delivery of the pharmaceutical compositions in the form of an aerosol or dry powder dispersion, to a mammal in need of treatment.

The present invention is still further concerned with the combination of the above-mentioned device and the package inserted therein, wherein the device is a metered dose inhaler, or a dry powder inhaler.

Detailed Description of the Invention

In its broadest terms, the present invention relates to a combination of two different groups of compounds. Each group of compounds is drawn from a different source, known in the art to have a different mechanism of action and a different therapeutic usefulness. The members of the first group of compounds are known in the art to be adenosine A_{2A} receptor agonists and to be useful as nervous system agents for treating, *e.g.*, Parkinson's disease, depression, schizophrenia, Tourette's syndrome, and drug abuse. The first the group of compounds has not been known in the art heretofore to be useful as monotherapy for the treatment of obstructive airways and other inflammatory diseases, including especially COPD and asthma.

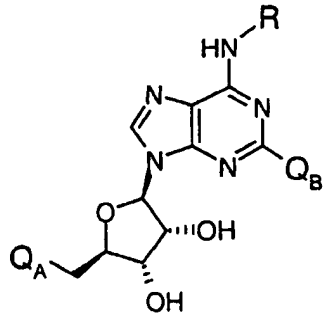
The members of the second group of compounds consist of a small subgenus of tiotropium-based compounds known in the art to be anti-cholinergic agents that selectively antagonize M_3 muscarinic receptors and to be useful as respiratory agents for treating bronchoconstriction associated with obstructive airways diseases.

Once a component candidate for prospective use in the combination of therapeutic agents of the present invention has been selected from each source consisting of the above-described group of compounds, it must satisfy one further test. It will be appreciated that members of each the group of compounds selected for use in the combination must satisfy the criterion that they be therapeutically effective in the treatment of obstructive airways and other inflammatory diseases as described herein when administered by inhalation. Procedures and assays for determining such therapeutic effectiveness are well known in the art, and some of these are described in detail further herein.

The Adenosine A_{2A} receptor Agonist Component

The present invention concerns combinations of therapeutic agents in which one of the agents is an adenosine A_{2A} receptor agonist, which is broadly defined herein to be one which has therapeutic activity in treating obstructive airways and other inflammatory diseases, especially COPD and asthma, when administered to a patient by means of inhalation. Within the scope of this group of adenosine A_{2A} receptor agonist agents that are suitable for use in the

combinations of compounds of the present invention, there is of particular interest adenosine A_{2A} receptor agonists that comprise a compound of Formula (3.0.1):



(3.0.1)

wherein:

$-Q_A$ is $-OR^1$; $-C(=O)NHR^3$; $-R^5$; or $-R^7$;

— wherein —

R^1 is -H; (C_1-C_4) alkyl; or cyclopropylmethyl;

R^3 is -H; (C_1-C_6) alkyl; (C_3-C_7) cycloalkyl; cyclopropylmethyl; phenyl; naphthyl, azetidin-3-yl; pyrrolidin-3-yl; piperidin-3-yl; piperidin-4-yl; or HET; where the azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl are substituted by 0 or 1 of (C_1-C_6) alkyl; and

— where —

HET is C-linked pyrrolyl; imidazolyl; triazolyl; thienyl; furyl; thiazolyl; oxazolyl; thiadiazolyl; oxadiazolyl; pyridinyl; pyrimidinyl; pyridazinyl; pyrazinyl; indolyl; isoindolyl; quinolinyl; isoquinolinyl; benzimidazolyl; quinazolinyl; phthalazinyl; benzoxazolyl; or quinoxalinyl; each substituted by 0-3 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or halo;

R^5 is $-CH_2OH$; or $-C(=O)NR^{14}R^{16}$;

— where —

R^{14} and R^{16} are each independently -H; or (C_1-C_6) alkyl substituted by 0 or 1 of cyclopropyl;

R^7 is a C-linked, 5-membered aromatic heterocycle containing (a) 1-4 ring nitrogen atoms, or (b) 1-2 ring nitrogen atoms and 1 oxygen or 1 sulfur ring atom, where the heterocycle is substituted by 0 or 1 (C_1-C_6) alkyl substituted by 0 or 1 of phenyl, -OH, (C_1-C_6) alkoxy, or $-NR^{18}R^{20}$;

— where —

R^{18} and R^{20} are each independently -H; (C_1-C_6) alkyl; or taken together with the nitrogen atom to which they are attached, are azetidinyl, pyrrolidinyl, or piperidinyl, each substituted by 0 or 1 of (C_1-C_6) alkyl;

— and —

$-Q_B$ is $-(CH_2)_n$-A-R^9; $-C(=O)N(R^{11})$-B-R^{13}; $-CH_2$-$NHS(=O)_2$-B-R^{15}; or -L-D-$N(R^{17})$-E-$NR^{19}R^{21}$;

— wherein —

n is 1 or 2;

A is $-NR^{22}$-; $-NR^{22}C(=O)$-; $-NR^{22}C(=O)NR^{24}$-; $-NR^{22}C(=O)O$-; $-OC(=O)NR^{22}$-; $-C(=O)NR^{22}$-; $-NR^{22}S(=O)_2$-; $-S(=O)_2NR^{22}$-; -O-; -S-; or $-S(=O)_2$-;

— where —

R^{22} and R^{24} are each independently -H; (C_1-C_4) alkyl; or benzyl substituted by 0-3 of (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo, or cyano;

R^9 is a group of the formula $-(CH_2)_p$-R^{26}-W;

— where —

p is 0, 1, or 2;

R^{26} is a bond; (C_1-C_4) alkylene; (C_3-C_7) cycloalkylene; phenylene; or naphthylene; the cycloalkylene, phenylene and naphthylene each being substituted by 0-3 of (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo, or (C_1-C_4) alkoxy(C_1-C_4) alkylene;

W is a member selected from the group consisting of:

(a) -H; $-NR^{28}R^{30}$; $R^{28}R^{30}N$-alkylene-; $-OR^{28}$; $-C(=O)OR^{28}$; $-OC(=O)R^{28}$; $-S(=O)_2R^{28}$; -CN; $-S(=O)_2NR^{28}R^{30}$; $-NR^{28}C(=O)R^{30}$; $-NR^{28}S(=O)_2R^{30}$; or $-C(=O)NR^{28}R^{30}$;

— where —

R^{28} and R^{30} are the same or different and are selected from the group consisting of -H, (C_1-C_4) alkyl, phenyl and benzyl;

— provided that —

(i) when W is $-OC(=O)R^{28}$, $-S(=O)_2R^{28}$, $-NR^{28}C(=O)R^{30}$, or $-NR^{28}S(=O)_2R^{30}$, then the terminal R^{30} is not -H; and,

(ii) R^{26} is a bond, p is 0, and W is -H only when A is $-NR^{22}$, $-NR^{22}C(=O)NR^{24}$, $-OC(=O)NR^{22}$, $-C(=O)NR^{22}$, $-S(=O)_2NR^{22}$, -O-, or -S-;

(b) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R^{26} by a ring carbon atom;

— and —

(c) N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each substituted by 0-3 (C_1-C_4) alkyl; with the proviso that $-(CH_2)_p-R^{26}$ is not $-CH_2-$; and

where:

A is $-NR^{22}-$, $-C(=O)NR^{22}-$, $-OC(=O)NR^{22}-$, or $-S(=O)_2NR^{22}-$; R^{22} and R^9 may be taken together with the nitrogen atom to which they are attached to form an azetidine, pyrrolidine, piperidine or piperazine ring, substituted by 0-3 of (C_1-C_4) alkyl;

R^{11} is -H; or (C_1-C_6) alkyl;

B is a bond; or (C_1-C_6) alkylene; and

R^{13} is a member selected from the group consisting of:

(a) -H; (C_1-C_6) alkyl; $-C(=O)OR^{32}$; -CN; $-C(=O)NR^{32}R^{34}$; -(C_3-C_8) cycloalkyl; phenyl; or naphthyl, where the -(C_3-C_8) cycloalkyl, phenyl, or naphthyl is substituted by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_1-C_6)alkyl, $R^{32}R^{34}N(C_1$-C_6)alkyl, halo(C_1-C_6)alkyl, fluoro(C_1-C_6)alkoxy, (C_2-C_5) alkanoyl, halo, $-OR^{32}$, cyano, $-C(=O)OR^{32}$, (C_3-C_8) cycloalkyl, $-S(=O)_mR^{35}$ where m is 0, 1, or 2, $-NR^{32}R^{34}$, $-S(=O)_2NR^{32}R^{34}$, $-C(=O)NR^{32}R^{34}$, $-NR^{32}C(=O)R^{35}$, or $-NR^{32}S(=O)_2R^{35}$; with the proviso that R^{13} is not -H when B is a bond;

(b) $-NR^{32}R^{34}$; $-OR^{32}$; $-C(=O)OR^{32}$; $-OC(=O)R^{34}$; $-S(=O)_2R^{34}$; -CN; $-S(=O)_2NR^{32}R^{34}$; $-NR^{32}COR^{34}$; or $-C(=O)NR^{32}R^{34}$; when B is (C_2-C_6) alkylene;

(c) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle having either from 1 to 4 ring nitrogen atom(s), or 1 or 2 nitrogen and 1 oxygen or 1 sulfur ring atoms;

C-substituted by 0-2 of oxo, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $R^{36}R^{38}N(C_1$-C_6) alkyl, halo(C_1-C_6) alkyl, fluoro(C_1-C_6) alkoxy, fluoro(C_2-C_5) alkanoyl, halo, cyano, $-OR^{36}$, $-R^{37}$, $-C(=O)R^{36}$, $-NR^{36}R^{38}$, $-C(=O)OR^{36}$, $-S(=O)_mR^{37}$ where m is 0, 1, or 2, $-S(=O)_2NR^{36}R^{38}$, $-C(=O)NR^{36}R^{38}$, $-NR^{36}S(=O)_2R^{37}$, or $-NR^{36}C(=O)R^{37}$; and

N-substituted by 0-2 of (C_1-C_6) alkoxy(C_1-C_6) alkyl, $R^{36}R^{38}N(C_2$-C_6) alkyl, halo(C_1-C_6) alkyl, fluoro(C_2-C_5) alkanoyl, $-R^{37}$, $-C(=O)R^{36}$, $-C(=O)OR^{37}$, $-S(=O)_2R^{37}$, $-S(=O)_2NR^{36}R^{38}$, or $-C(=O)NR^{36}R^{38}$;

— and —

(d) N-linked azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; homopiperazinyl; or morpholinyl; when B is C_2-C_6 alkylene;

each C-substituted by 0-2 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_1-C_6) alkyl, $R^{32}R^{34}N$(C_1-C_6) alkyl, halo(C_1-C_6) alkyl, fluoro(C_1-C_6) alkoxy, (C_2-C_5) alkanoyl, halo, $-OR^{32}$, cyano, $-C(=O)OR^{32}$, (C_3-C_8) cycloalkyl, $-S(=O)_mR^{35}$ where m is 0, 1, or 2, $-NR^{32}R^{34}$, $-S(=O)_2NR^{32}R^{34}$, $-C(=O)NR^{32}R^{34}$, $-NR^{32}C(=O)R^{35}$, or $-NR^{32}S(=O)_2R^{35}$; and

each the piperazinyl or homopiperazinyl N-substituted by 0-2 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_2-C_6) alkyl, $R^{32}R^{34}N$(C_2-C_6) alkyl, fluoro(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, $-C(=O)OR^{35}$, (C_3-C_8) cycloalkyl, $-S(=O)_2R^{35}$, $-S(=O)_2NR^{32}R^{34}$, or $-C(=O)NR^{32}R^{34}$;

— where —

R^{32} and R^{34} are each independently -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl; or R^{32} and R^{34} are taken together with the nitrogen atom to which they are attached to form azetidinyl; pyrrolidinyl; piperidinyl; morpholinyl; piperazinyl; homopiperidinyl; homopiperazinyl; or tetrahydroisoquinolinyl; each substituted on a ring carbon atom by 0 or 1 of (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, phenyl, (C_1-C_6) alkoxy-(C_1-C_6) alkyl, $R^{54}R^{56}N$-(C_1-C_6) alkyl, fluoro-(C_1-C_6) alkyl, $-C(=O)NR^{54}R^{56}$, $-C(=O)OR^{54}$, or (C_2-C_5) alkanoyl; further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0 or 11 of fluoro-(C_1-C_6) alkoxy, halo, $-OR^{54}$, cyano, $-S(=O)_mR^{55}$, $-NR^{54}R^{56}$, $-S(=O)_2NR^{54}R^{56}$, $-NR^{54}C(=O)R^{55}$, or $-NR^{54}S(=O)_2R^{55}$; and the piperazin-1-yl and homopiperazin-1-yl are substituted on the secondary nitrogen atom by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy-(C_2-C_6) alkyl, $R^{54}R^{56}N$(C_2-C_6) alkyl, fluoro(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, $-C(=O)OR^{55}$, (C_3-C_6) cycloalkyl, $-S(=O)_2R^{55}$, $-S(=O)_2NR^{54}R^{56}$, or $-C(=O)NR^{54}R^{56}$;

R^{35} is (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl;

R^{36} and R^{38} are each independently -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; phenyl; naphthyl; or HET where HET has the same meaning as defined above;

— and —

R^{37} is (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; phenyl; naphthyl; or HET where HET has the same meaning as defined above;

R^{15} has the same meaning as parts (a), (b), and (c) of R^{13} defined above, including all sub-substituents thereof;

L is a bond or a linking group $-C(=O)NR^{40}$, where R^{40} has the same meaning as R^{11} defined above;

D is $-CH_2-$; $-CH_2CH_2-$; or $-CH_2CH_2CH_2-$; each substituted by 0 or 1 of (C_1-C_6) alkyl, or (C_3-C_8) cycloalkyl;

E is $-C(=O)-$; $-C(=S)-$; $-S(=O)_2-$; or $-C[=N(CN)]-$;

R^{17} has the same meaning as R^{11} defined above;

R^{19} is -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or benzyl;

R^{21} is azetidin-3-yl; pyrrolidin-3-yl; piperidin-3-yl; piperidin-4-yl; homopiperidin-3-yl; or homopiperidin-4-yl; each substituted by 0-2 of (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or benzyl; or $-(C_2-C_6)$ alkylene-R^{42}; or $-(C_1-C_6)$ alkylene-R^{44};

— or —

R^{19} and R^{21} are taken together with the nitrogen atom to which they are attached to form azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; homopiperidinyl; or homopiperazinyl; each substituted on a ring nitrogen or carbon atom by 0-3 of (C_1-C_6) alkyl, or (C_3-C_8) cycloalkyl; and further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0-3 of $-NR^{46}R^{48}$;

— where —

R^{42} is $NR^{50}R^{52}$; or azetidin-1-yl; pyrrolidin-1-yl; piperidin-1-yl; morpholin-4-yl; piperazin-1-yl; homopiperidin-1 -yl; homopiperazin-1-yl; or tetrahydroisoquinolin-1-yl; each substituted on a ring carbon atom by 0 or 1 (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, phenyl, (C_1-C_6) alkoxy-(C_1-C_6) alkyl, $R^{54}R^{56}N$-(C_1-C_6) alkyl, fluoro-(C_1-C_6) alkyl, $-C(=O)NR^{54}R^{56}$, $-C(=O)OR^{54}$, or (C_2-C_5) alkanoyl; and further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0 or 1 of fluoro(C_1-C_6) alkoxy, halo, $-OR^{54}$, cyano, $-S(=O)_mR^{55}$, $-NR^{54}R^{56}$, $-S(=O)_2NR^{54}R^{56}$, $-NR^{54}C(=O)R^{55}$, or $-NR^{54}S(=O)_2R^{55}$; and further the piperazin-1-yl and homopiperazin-1-yl are substituted on the ring nitrogen atom not attached to the (C_2-C_6) alkylene group by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy-(C_2-C_6) alkyl, $R^{54}R^{56}N$-(C_2-C_6) alkyl, fluoro-(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, $-C(=O)OR^{55}$, (C_3-C_8) cycloalkyl, $-S(=O)_2R^{55}$, $-S(=O)_2NR^{54}R^{56}$, or $-C(=O)NR^{54}R^{56}$;

R^{44} is phenyl; pyridin-2-yl; pyridin-3-yl; or pyridin-4-yl; each substituted by 0 or 1 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, or cyano;

R^{46} and R^{48} are each independently -H; or (C_1-C_6) alkyl; or, taken together with the nitrogen atom to which they are attached, represent azetidinyl, pyrrolidinyl, or piperidinyl; each substituted by 0 or 1 of (C_1-C_6) alkyl;

R^{50} is -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or benzyl;

R^{52} is -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; phenyl; benzyl; fluoro-(C_1-C_6) alkyl; $-C(=O)NR^{54}R^{56}$; $-C(=O)OR^{55}$; (C_2-C_5) alkanoyl; or $-S(=O)_2NR^{54}R^{56}$;

R^{54} and R^{56} are each independently -H; (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl;

R^{55} is (C_1-C_6) alkyl; (C_3-C_8) cycloalkyl; or phenyl;

-R is -H; (C_1-C_6) alkyl; or fluorenyl; where the (C_1-C_6) alkyl is substituted by 0-2 of phenyl, or naphthyl; where the phenyl or naphthyl is substituted by 0 or 2 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, or cyano;

or a pharmaceutically acceptable salt thereof.

Preferred embodiments of the present invention comprise combinations of therapeutic agents as described herein wherein, in particular, the adenosine A_{2A} receptor agonist is a member selected from the group consisting of the following:

9-[(2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-2-phenylacetamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzenesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-[2-(benzylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-(cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-{[(cyclohexylmethyl)amino]methyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-[(cyclopentylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-1-propanesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-{2-[2-(cyclohexylamino)ethyl]-6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-(2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)benzenesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[2-(isopropylamino)ethyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperdinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-phenylethyl-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(4-isopropyl-1-piperdinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[3-(1-pyrrolidinyl)propyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(4-morpholinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-(2-pyridinylmethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(2-pyridinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-*N*-[2-(dimethylamino)ethyl]-6-[(2,2-diphenylethyl)amino]- 9*H*-purine-2-carboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-(phenylethylamino)-9*H*-purin-2-yl]methyl}benzenesulfonamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purin-2-yl}methyl)benzenesulfonamide;

2-[cyclopentyl(isopropyl)amino]-*N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-ethanesulfonamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[(benzylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(propylsulfonyl)amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(isopropylsulfonyl)amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(phenylsulfonyl)amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[([1,1'-biphenyl]-4-ylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(naphthylsulfonyl)amino]-methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-di-isopropylamino)ethyl]urea;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-(1-piperidinyl)ethyl]urea;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]-methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-{2-{[({[2-(1-piperidinyl)ethyl]-amino}-carbonyl)amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({6-{[2,2-bis(4-chlorophenyl)ethyl]amino}-9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-(2-di-isopropylamino)ethyl]urea;

N-[2-(dicyclobutylamino)ethyl]-N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)urea;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(4-isopropyl-1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

N-{2-[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]ethyl}-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-*N*-{2-[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]ethyl}-6-[(2,2-diphenylethyl)amino] -9*H*-purine-2-carboxamide;

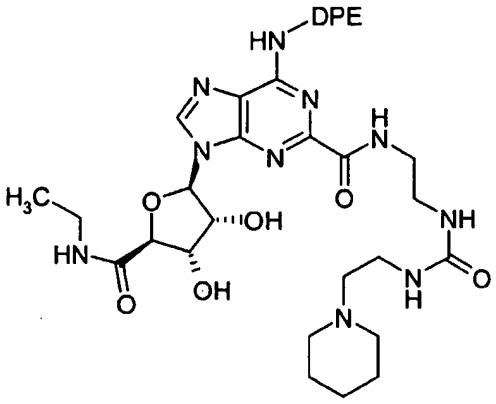
6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(4-isopropyl-1-piperidinyl)ethyl]amino}-carbonyl)-amino]ethyl}-9*H*-purine-2-carboxamide;

N-(2-{[({2-[cyclopentyl(isopropyl)amino]ethyl}amino)carbonyl]amino}ethyl)-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetra-hydro-2-furanyl}-9*H*-purine-2-carboxamide;

— and —

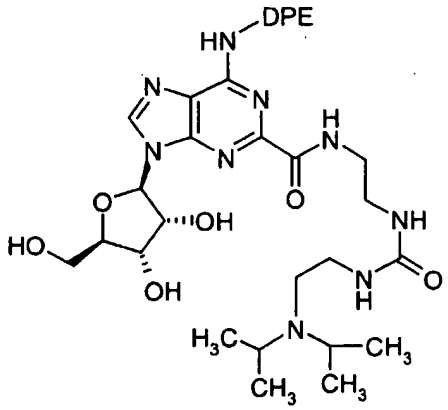
N-(2-{[({2-[cyclohexyl(isopropyl)amino]ethyl}amino)carbonyl]amino}ethyl)-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetra-hydro-2-furanyl}-9*H*-purine-2-carboxamide.

In order to further illustrate preferred embodiments of the present invention comprising specific adenosine A_{2A} receptor agonists for use as component compounds in the combinations of therapeutic agents of the present invention, there is set forth hereafter Formulas (3.0.2) through (3.0.46), in which DPE is used as an abbreviation for the moiety diphenylethyl-.



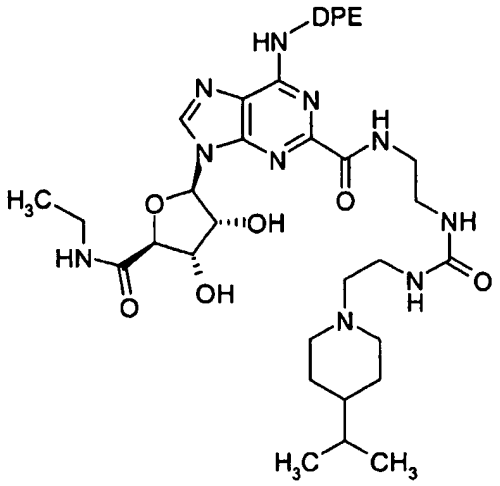
(3.0.2)

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)-amino]ethyl}-9*H*-purine-2-carboxamide



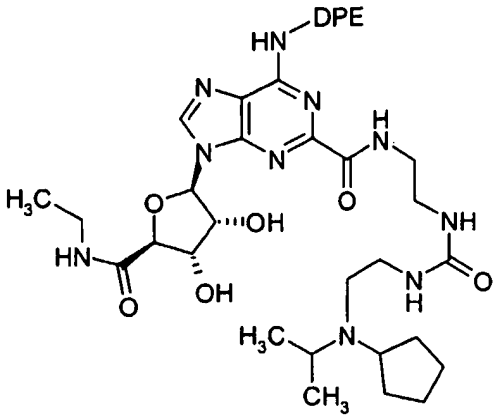
(3.0.3)

9-{(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-*N*-{2-[({[2-(diisopropylamino)ethyl]amino}-carbonyl)amino]-ethyl}-6-[(2,2-diphenyl-ethyl)-amino]-9*H*-purine-2-carboxamide



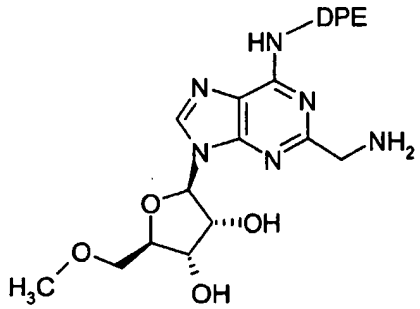
(3.0.4)

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(4-isopropyl-1-piperidinyl)ethyl]amino}-carbonyl)-amino]ethyl}-9*H*-purine-2-carboxamide



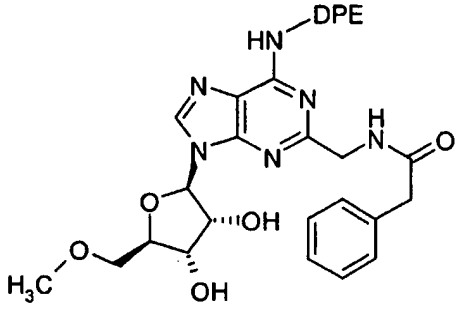
(3.0.5)

N-(2-{[({2-[cyclopentyl(isopropyl)amino]-ethyl}-amino)carbonyl]amino}ethyl)-6-[(2,2-diphenyl-ethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethyl-amino)carbonyl]-3,4-dihydroxy-tetrahydro-2-furanyl}-9*H*-purine-2-carboxamide



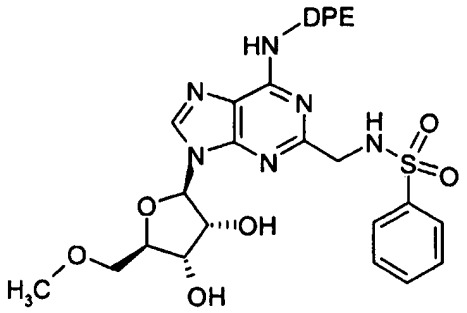
(3.0.6)

9-[(2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



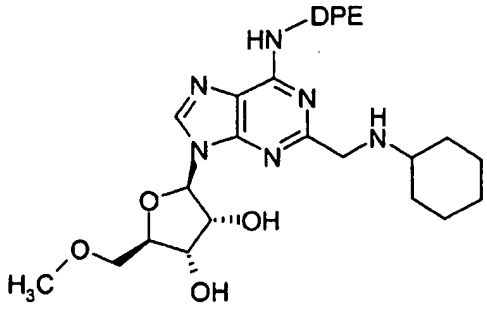
(3.0.7)

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahy-dro-2-furanyl]-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-2-yl]methyl}-2-phenylacetamide



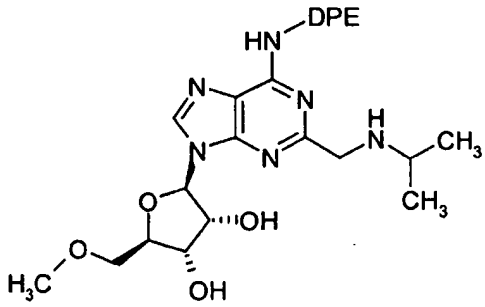
(3.0.8)

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-benzenesulfonamide



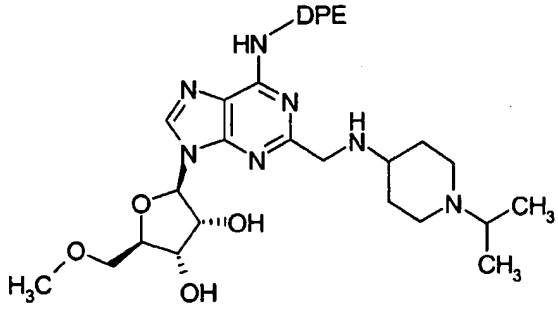
(3.0.9)

(2*R*,3*R*,4*S*,5*R*)-2-[2-(cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol



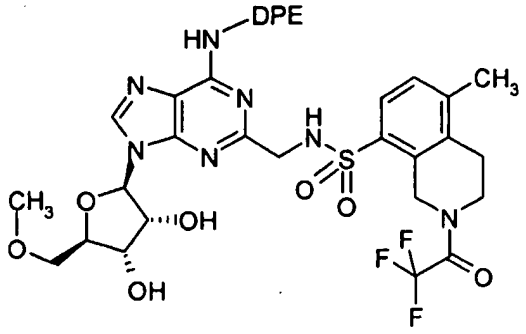
(3.0.10)

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



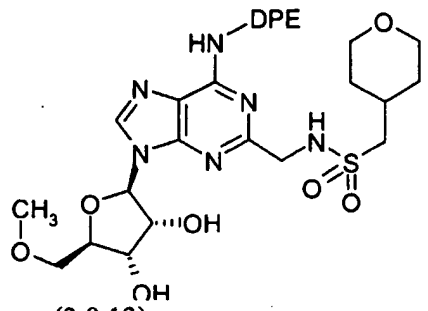
(3.0.11)

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)-amino]-2-{[(1-isopropyl-4-piperidinyl)amino]-methyl}-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol



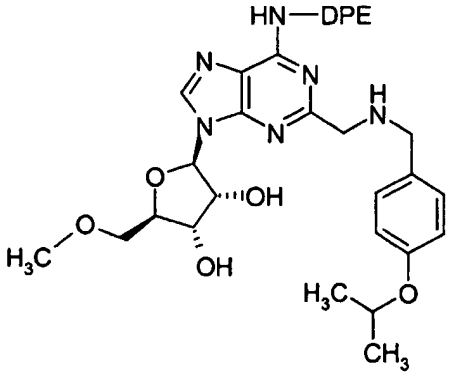
(3.0.12)

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-5-methyl-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydro-8-isoquinolinesulfonamide



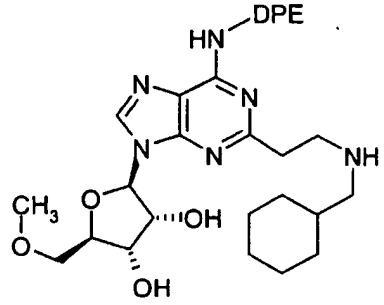
(3.0.13)

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)(tetrahydro-2*H*-pyran-4-yl)methane-sulfonamide



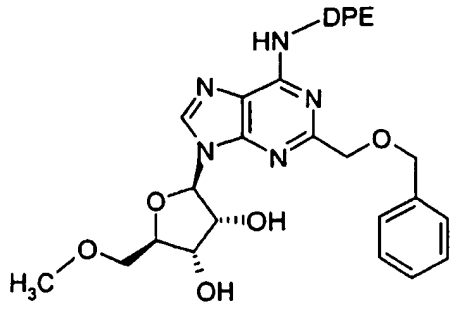
(3.0.14)

(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)-amino]-2-{[(4-isopropoxybenzyl)amino]-methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)-tetrahydro-3,4-furandiol



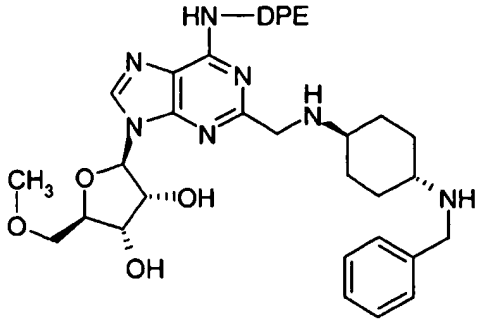
(3.0.15)

(2*R*,3*R*,4*S*,5*R*)-2-{2-{2-[(cyclohexyl-methyl)-amino]ethyl}-6-[(2,2-diphenyl-ethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



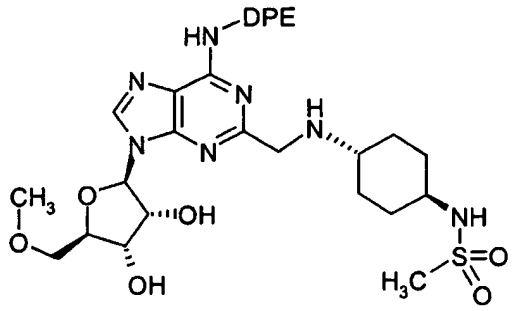
(3.0.16)

(2*R*,3*R*,4*S*,5*R*)-2-{2-[(benzyloxy)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



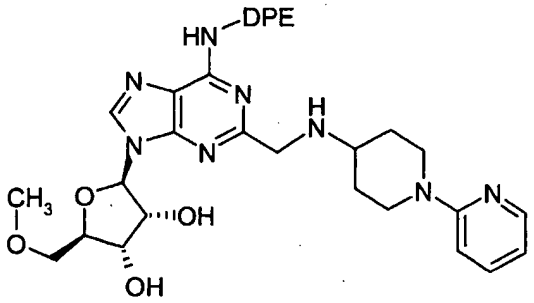
(3.0.17)

(2*R*,3*R*,4*S*,5*R*)-2-{2-({[*trans*-4-(benzylamino)-cyclohexyl]amino}methyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxy-methyl)tetrahydro-3,4-furandiol



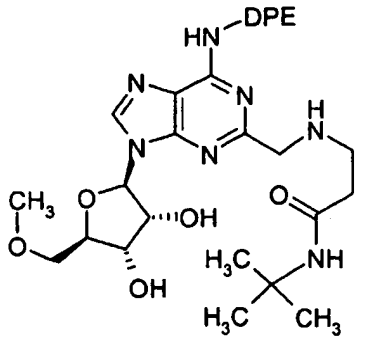
(3.0.18)

N-{4-[({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-amino]*trans*-cyclohexyl}methanesulfonamide



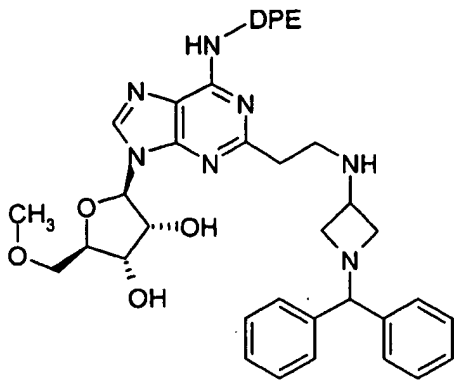
(3.0.19)

(2*R*,3*R*,4*S*,5*R*)-2-[6-[(2,2-diphenylethyl)-amino]-2-({[1-(2-pyridinyl)-4-piperidinyl]-amino}methyl)-9*H*-purin-9-yl]-5-(methoxy-methyl)tetrahydro-3,4-furandiol



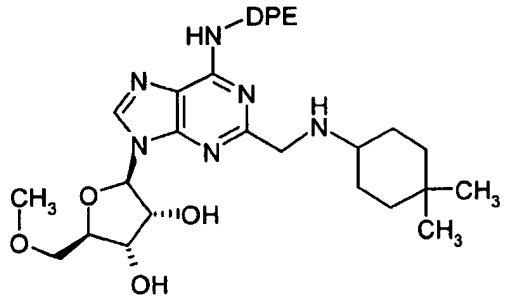
(3.0.20)

N-(*tert*-butyl)-3-[({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)amino]propanamide



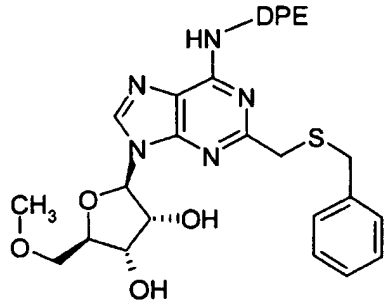
(3.0.21)

(2*R*,3*R*,4*S*,5*R*)-2-{2-{2-[(1-benzhydryl-3-azetidinyl)amino]ethyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol



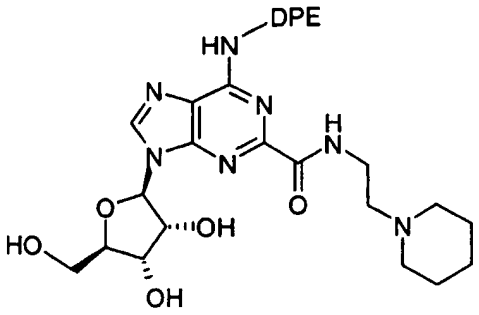
(3.0.22)

(2*R*,3*R*,4*S*,5*R*)-2-{2-{[(4,4dimethylcyclohexyl)-amino]methyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol



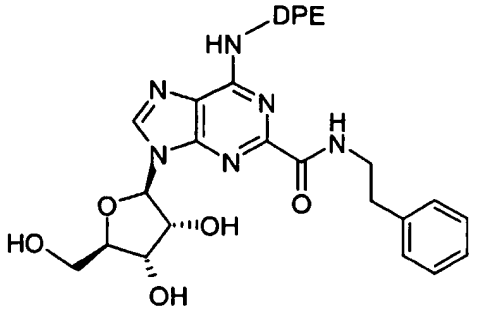
(3.0.23)

(2*R*,3*R*,4*S*,5*R*)-2-{2-[(benzyl-sulfanyl)methyl]-6-[(2,2-diphenyl-ethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



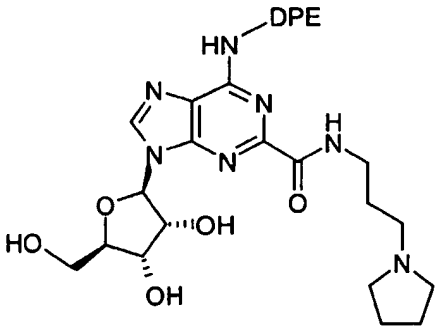
(3.0.24)

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-6-[(2,2-diphenyl-ethyl)amino]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide



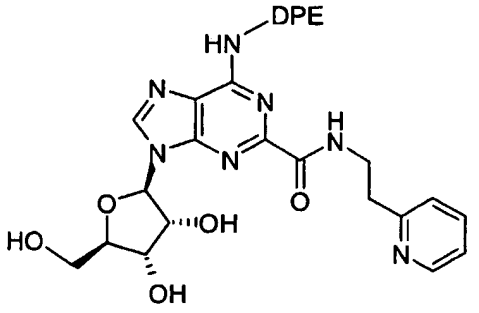
(3.0.25)

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-6-[(2,2-diphenyl-ethyl)amino]-*N*-phenethyl-9*H*-purine-2-carboxamide



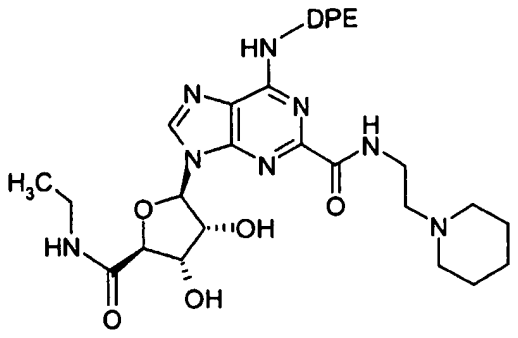
(3.0.26)

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-6-[(2,2-diphenyl-ethyl)amino]-*N*-[3-(1-pyrrolidinyl)propyl]-9*H*-purine-2-carboxamide



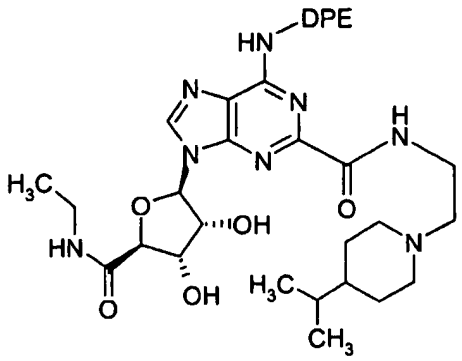
(3.0.27)

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-6-[(2,2-diphenyl-ethyl)amino]-*N*-[2-(2-pyridinyl)ethyl]-9*H*-purine-2-carboxamide



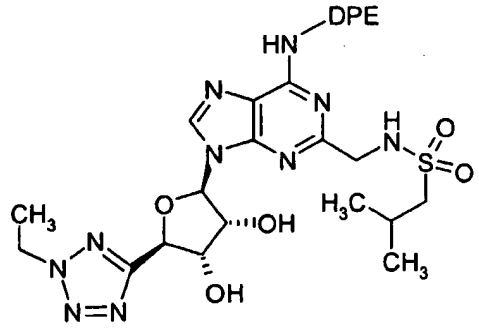
(3.0.28)

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide



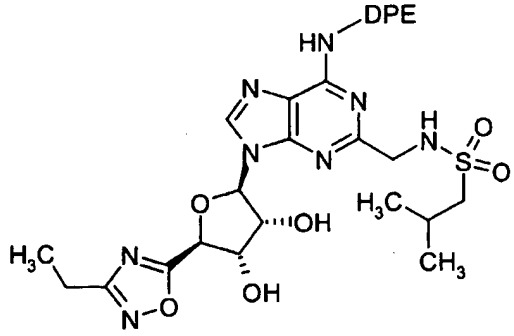
(3.0.29)

6-[(2,2-diphenylethyl)amino]-9-{(2R,3R,4S,5S)-5-[(ethylamino)-carbonyl]-3,4-dihydroxy-tetrahydro-2-furanyl}-*N*-[2-(4-isopropyl-1-piperi-dinyl)ethyl]-9*H*-purine-2-carboxamide



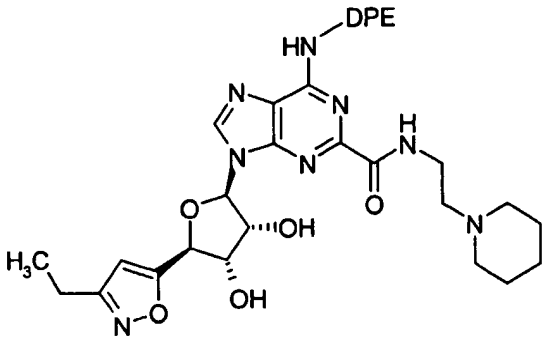
(3.0.30)

N-({6-[(2,2-diphenyl-ethyl)amino]-9-[(2*R*,3*R*,4*S*,5*R*)-5-(2-ethyl-2*H*-tetrazol-5-yl)-3,4-dihydroxytetrahydro-2-furanyl]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide



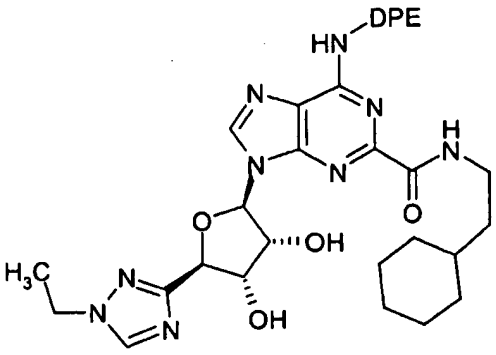
(3.0.31)

N-({6-[(2,2-diphenyl-ethyl)amino]-9-[(2R,3R,4S,5S)-5-(3-ethyl-1,2,4-oxadiazol-5-yl)-3,4-dihydroxytetra-hydro-2-furanyl]-9*H*-purin-2-yl}-methyl)-2-methyl-1-propanesulfonamide



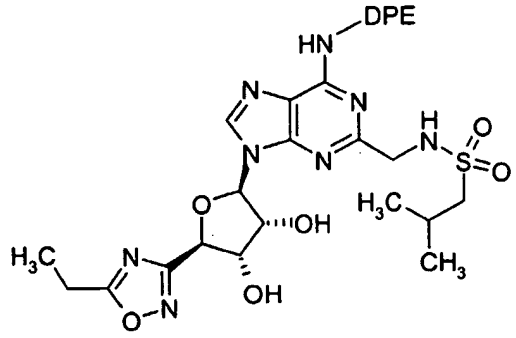
(3.0.32)

6-[(2,2-diphenyl-ethyl)amino]-9-[(2*R*,3*R*,4*S*,5*S*)-5-(3-ethyl-5-isoxazolyl)-3,4-dihydroxytetrahydro-2-furanyl]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide



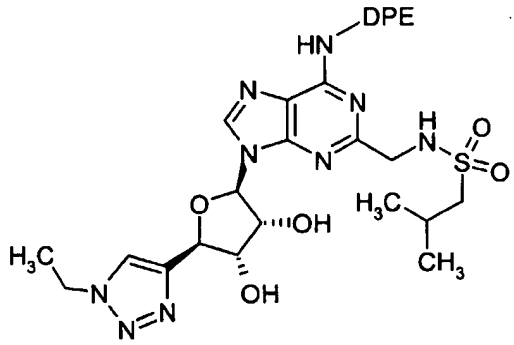
(3.0.33)

6-[(2,2-diphenyl-ethyl)amino]-9-[(2*R*,3*R*,4*S*,5*R*)-5-(1-ethyl-1*H*-1,2,4-triazol-5-yl)-3,4-dihydroxytetrahydro-2-furanyl]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide



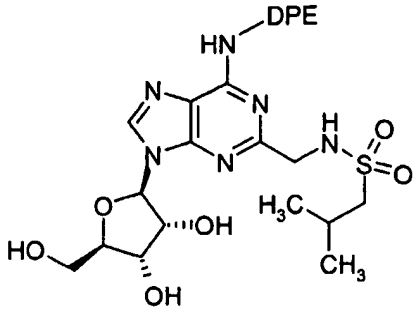
(3.0.34)

N-({6-[(2,2-diphenyl-ethyl)amino]-9-[(2*R*,3*R*,4*S*,5*R*)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-3,4-dihydroxytetrahydro-2-furanyl]-9*H*-purin-2-yl}methyl)-2-methyl-1-propane-sulfonamide



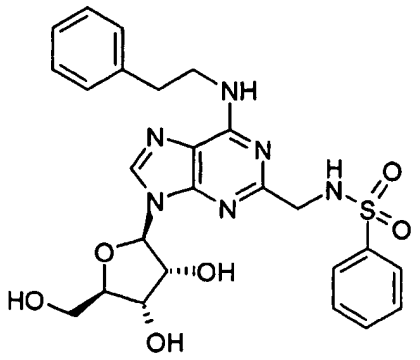
(3.0.35)

N-({6-[(2,2-diphenyl-ethyl)amino]-9-[(2*R*,3*R*,4*S*,5*R*)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-3,4-dihydroxytetrahydro-2-furanyl]-9*H*-purin-2-yl}methyl)-2-methyl-1-propane-sulfonamide



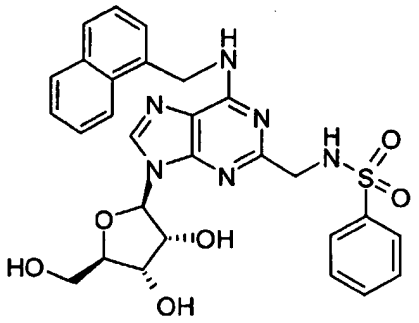
(3.0.36)

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide



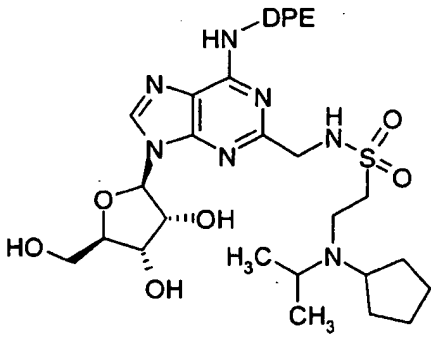
(3.0.37)

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-(phenylethylamino)-9*H*-purin-2-yl]-methyl}-benzenesulfonamide



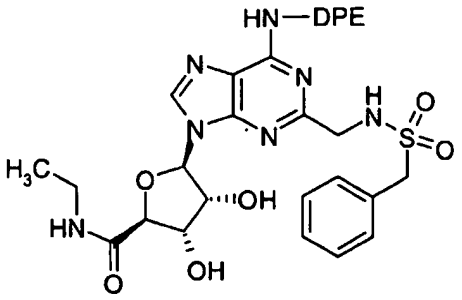
(3.0.38)

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purin-2-yl}methyl)-benzenesulfonamide



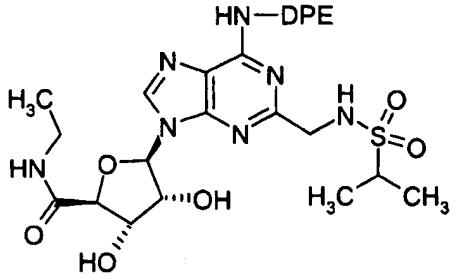
(3.0.39)

2-[cyclopentyl(isopropyl)amino]-*N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-6-[(2,2-diphenyl-ethyl)amino]-9*H*-purin-2-yl}methyl)-ethane-sulfonamide



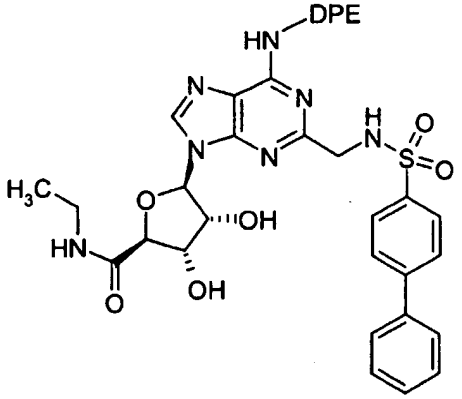
(3.0.40)

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[(benzylsulfonyl)amino]-methyl}-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide



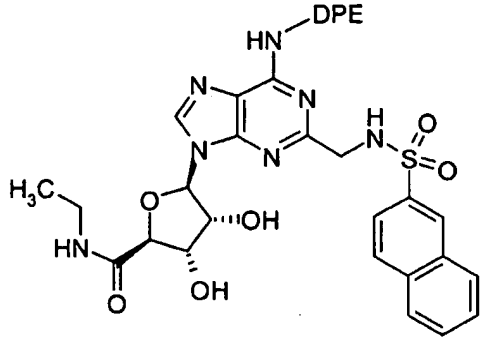
(3.0.41)

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)-amino]-2-{[(isopropylsulfonyl)-amino]-methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxy-tetrahydro-2-furancarb-oxamide



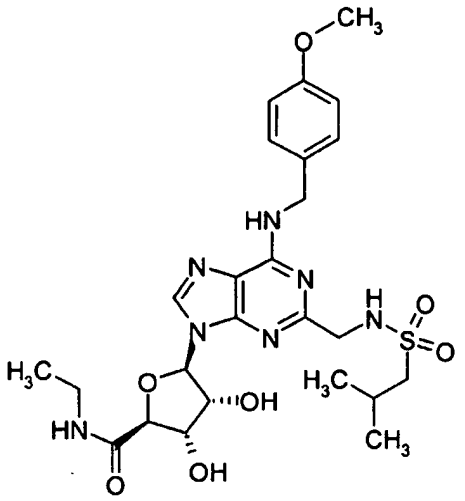
(3.0.42)

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[([1,1'-biphenyl]-4-ylsulfonyl)amino]methyl}-6-[(2,2-diphenyl-ethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide



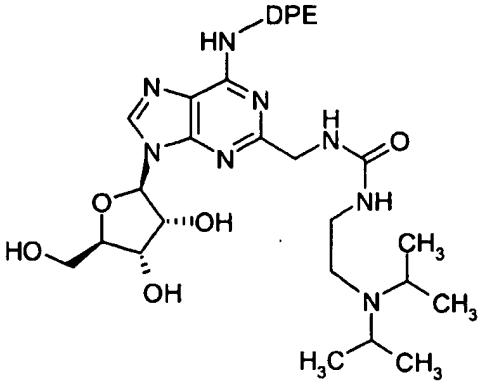
(3.0.43)

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)-amino]-2-{[(2-naphthylsulfonyl)-amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxy-tetrahydro-2-furancarb-oxamide



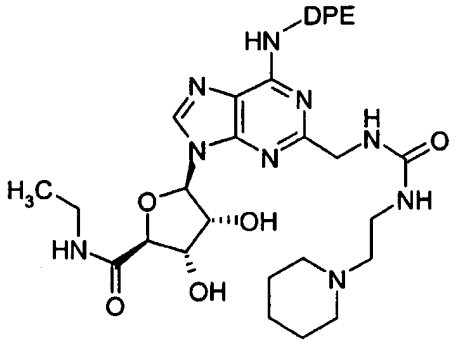
(3.0.44)

(2*S*,3*S*,4*R*,5*R*)-*N*-ethyl-3,4-dihydroxy-5-{2-{[(isobutylsulfonyl)amino]methyl}-6-[(4-methoxybenzyl)-amino]-9*H*-purin-9-yl}-tetrahydro-2-furancarboxamide



(3.0.45)

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-di-isopropylamino)-ethyl]urea

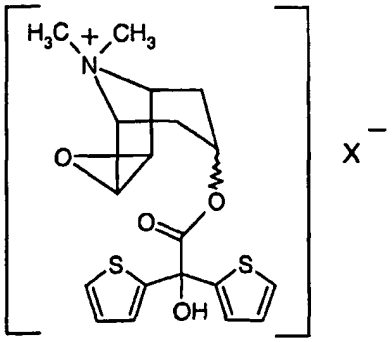


(3.0.46)

(2*R*,3*R*,4*S*,5*R*)-5-(6-[(2,2-diphenylethyl)-amino]-2-{[({[2-(1-piperidinyl)-ethyl]amino}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide.

The Anti-Cholinergic Agent Component

The second component of the combination of therapeutic agents of the present invention comprises an anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective in the treatment of obstructive airways and other inflammatory diseases as described herein when administered by inhalation. The anti-cholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof is a compound of Formula (1.1.1):



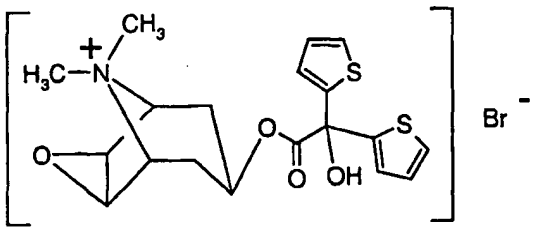
(1.1.1)

wherein X^- is a physiologically acceptable anion. Most commonly, such a physiologically acceptable anion will be a halogen anion, but a number of other suitable physiologically acceptable anions would suggest themselves to the medicinal chemist of ordinary skill in the art of preparing such therapeutic agents. In preferred embodiments of the subgenus of tiotropium-based anti-cholinergic agents the physiologically acceptable anion is selected from the group consisting of fluoride, F^-; chloride, Cl^-; bromide, Br^-; iodide, I^-; methanesulfonate, $CH_3S(=O)_2O^-$; ethanesulfonate, $CH_3CH_2S(=O)_2O^-$; methylsulfate, $CH_3OS(=O)_2O^-$; benzene sulfonate, $C_6H_5S(=O)_2O^-$; *p*-toluenesulfonate, and 4-CH_3-$C_6H_5S(=O)_2O^-$. In more preferred embodiments the physiologically acceptable anion is selected from the group consisting of chloride, Cl^-; and bromide, Br^-. In the most preferred embodiments of the present invention, the physiologically acceptable anion is bromide, Br^-.

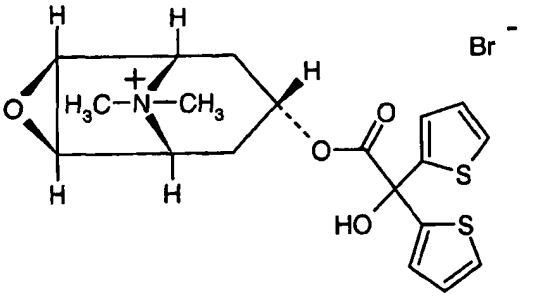
In addition to the choice of physiologically acceptable anion, it will be appreciated that the anti-cholinergic agent comprising a member selected from the group consisting of tiotropium

and derivatives thereof represented by Formula (1.1.1) presents a choice with respect to whether the compounds are 3α or 3β compounds. This choice is represented by the non-specific bond (wavy bond) in Formula (1.1.1). The members of the subgenus having an α-configuration are preferred. It is also preferred that the epoxy group have a 6β, 7β-configuration.

Taking into consideration all of the above-described preferred aspects of members of the group consisting of tiotropium and derivatives thereof comprising one of the components of the combination of the present invention, the most preferred species member of the group is tiotropium bromide. Tiotropium bromide may be named as (1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]-nonane bromide, or as 6β,7β-epoxy-3β-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide, di-2-thienylglycolate. These names are based on different nomenclature systems, but identify the same compound, which is referred to herein as tiotropium bromide. Tiotropium bromide may be represented by either Formula (1.1.2) or by Formula (1.1.3):

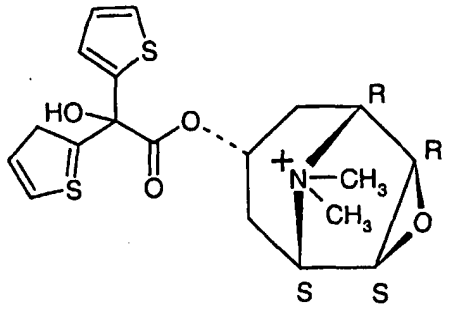


(1.1.2)



(1.1.3)

The relative stereochemistry of tiotropium bromide may also be shown by Formula (1.1.4):



(1.1.4)

Pharmaceutical Salts and Other Forms

The individual components of the above-described combinations of compounds of the present invention may be utilized in their final, non-salt form. On the other hand, it is also within the scope of the present invention to utilize those component compounds in the form of their pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures well known in the art.

Pharmaceutically acceptable salt forms of the combinations of compounds of the present invention are prepared for the most part by conventional means. Where the component compound contains a carboxylic acid group, a suitable salt thereof may be formed by reacting the compound with an appropriate base to provide the corresponding base addition salt. Examples of such bases are alkali metal hydroxides including potassium hydroxide, sodium hydroxide, and lithium hydroxide; alkaline earth metal hydroxides such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, *e.g.*, potassium ethanolate and sodium propanolate; and various organic bases such as piperidine, diethanolamine, and *N*-methylglutamine. Also included are the aluminum salts of the component compounds of the present invention.

For certain component compounds acid addition salts may be formed by treating the compounds with pharmaceutically acceptable organic and inorganic acids, *e.g.*, hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding

salts such as sulfate, nitrate, phosphate, etc.; and alkyl- and mono-arylsulfonates such as ethanesulfonate, toluenesulfonate, and benzenesulfonate; and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate, etc.

Accordingly, the pharmaceutically acceptable acid addition salts of the component compounds of the present invention include, but are not limited to: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate.

Further, base salts of the component compounds of the present invention include, but are not limited to aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, and zinc salts. Preferred among the above-recited salts are ammonium; the alkali metal salts sodium and potassium; and the alkaline earth metal salts calcium and magnesium. Salts of the component compounds of the present invention derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, *e.g.*, arginine, betaine, caffeine, chloroprocaine, choline, *N,N'*-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins,

procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine, and tris-(hydroxymethyl)-methylamine (tromethamine).

Component compounds of the present invention which comprise basic nitrogen-containing groups may be quaternized with such agents as (C_1-C_4) alkyl halides, *e.g.*, methyl, ethyl, isopropyl and *tert*-butyl chlorides, bromides and iodides; di(C_1-C_4) alkyl sulfate, *e.g.*, dimethyl, diethyl and diamyl sulfates; (C_{10}-C_{18}) alkyl halides, *e.g.*, decyl, dodecyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aryl-(C_1-C_4) alkyl halides, *e.g.*, benzyl chloride and phenethyl bromide. Such salts permit the preparation of both water-soluble and oil-soluble compounds of the present invention.

Among the above-recited pharmaceutical salts those which are preferred include, but are not limited to acetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate, and tromethamine.

The acid addition salts of basic component compounds of the present invention are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base forms for purposes of the present invention.

As indicated, the pharmaceutically acceptable base addition salts of the component compounds of the present invention are formed with metals or amines, such as alkali metals and alkaline earth metals, or organic amines. Preferred metals are sodium, potassium, magnesium, and calcium. Preferred organic amines are *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, *N*-methyl-D-glucamine, and procaine

The base addition salts of acidic component compounds of the present invention are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid form in the conventional manner. The free acid forms differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms for purposes of the present invention.

Multiple salts forms are included within the scope of the present invention where a component compound of the present invention contains more than one group capable of forming such pharmaceutically acceptable salts. Examples of typical multiple salt forms include, but are not limited to bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium, and trihydrochloride.

In light of the above, it can be seen that the expression "pharmaceutically acceptable salt" as used herein is intended to mean an active ingredient comprising component compounds of the present invention utilized in the form of a salt thereof, especially where the salt form confers on the active ingredient improved pharmacokinetic properties as compared to the free form of the active ingredient or some other salt form of the active ingredient utilized previously. The pharmaceutically acceptable salt form of the active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which it did not previously possess, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body.

The pharmacokinetic properties of the active ingredient which may be favorably affected include, *e.g.*, the manner in which the active ingredient is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of the active ingredient.

A component compound prepared in accordance with the methods described herein can be separated from the reaction mixture in which it is finally produced by any ordinary means

known to the chemist skilled in the preparation of organic compounds. Once separated the compound can be purified by known methods. Various methods and techniques can be used as the means for separation and purification, and include, *e.g.*, distillation; recrystallization; column chromatography; ion-exchange chromatography; gel chromatography; affinity chromatography; preparative thin-layer chromatography; and solvent extraction.

Stereoisomers

In many cases, an adenosine A_{2A} receptor agonist or an anti-cholinergic agent, particularly tiotropium or a derivative thereof, that comprises a component part of the combinations of the present invention may be such that its constituent atoms are capable of being arranged in space in two or more different ways, despite having identical connectivities. As a consequence, such an active agent exists in the form of stereoisomers. *Cis-trans* isomerism is but one type of stereoisomerism. Where the stereoisomers are nonsuperimposable mirror images of each other, they are enantiomers which have chirality or handedness, because of the presence of one or more asymmetric carbon atoms in their constituent structure. Enantiomers are optically active and therefore distinguishable because they rotate the plane of polarized light by equal amounts, but in opposite directions.

Where two or more asymmetric carbon atoms are present in an active agent forming a part of a combination of the present invention, there are two possible configurations at each the carbon atom. Where two asymmetric carbon atoms are present, for example, there are four possible stereoisomers. Further, these four possible stereoisomers may be arranged into six possible pairs of stereoisomers that are different from each other. In order for a pair of molecules with more than one asymmetric carbon to be enantiomers, they must have different configurations at every asymmetric carbon. Those pairs that are not related as enantiomers have a different stereochemical relationship referred to as a diastereomeric relationship. Stereoisomers that are not enantiomers are called diastereoisomers, or more commonly, diastereomers.

All of these well known aspects of the stereochemistry of the active agents that form a part of a combination of the present invention are contemplated to be a part of the present invention. Within the scope of the present invention there is thus included active agents that are

stereoisomers, and where these are enantiomers, the individual enantiomers, racemic mixtures of the enantiomers, and artificial, *i.e.*, manufactured mixtures containing proportions of the enantiomers that are different from the proportions of the enantiomers found in a racemic mixture. Where an active agent forming part of a combination of the present invention comprises stereoisomers that are diastereomers, there is included within the scope of the active agent the individual diastereomers as well as mixtures of any two or more of the diastereomers in any proportions thereof.

By way of illustration, in the case where there is a single asymmetric carbon atom in an active agent of a combination of the present invention, resulting in the (-)(*R*) and (+)(*S*) enantiomers thereof; there is included within the scope of the active agent all pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active and useful in treating or preventing the diseases and conditions described further herein. Where an active agent of a combination of the present invention exists in the form of (-)(*R*) and (+)(*S*) enantiomers, there is also included within the scope of the active agent the (+)(*S*) enantiomer alone, or the (-)(*R*) enantiomer alone, in the case where all, substantially all, or a predominant share of the therapeutic activity resides in only one of the enantiomers, and/or unwanted side effects reside in only one of the enantiomers. In the case where there is substantially no difference between the biological activities of both enantiomers, there is further included within the scope of the active agent of a combination of the present invention the (+)(*S*) enantiomer and the (-)(*R*) enantiomer present together as a racemic mixture or as a non-racemic mixture in any ratio of proportionate amounts thereof.

For example, the particular biological activities and/or physical and chemical properties of a pair or set of enantiomers of an active agent of a combination of the present invention, where such exist, may suggest use of the enantiomers in certain ratios to constitute a final therapeutic product. By way of illustration, in the case where there is a pair of enantiomers, they may be employed in ratios such as 90% (*R*) - 10% (*S*); 80% (*R*) - 20% (*S*); 70% (*R*) - 30% (*S*); 60% (*R*) - 40% (*S*); 50% (*R*) - 50% (*S*); 40% (*R*) - 60% (*S*); 30% (*R*) - 70% (*S*); 20% (*R*) - 80% (*S*); and 10% (*R*) - 90% (*S*). After evaluating the properties of the various enantiomers of an active agent of a combination of the present invention, where such exist, the proportionate amount of

one or more of the enantiomers with certain desired properties that will constitute the final therapeutic product can be determined in a straightforward manner.

Isotopes

The present invention includes isotopically-labeled forms of the adenosine A_{2A} receptor agonist or the anti-cholinergic agent thereof. An isotopically-labeled form of an active agent of a combination of the present invention is identical to the active agent but for the fact that one or more atoms of the active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of the atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

An isotopically-labeled active agent of a combination of the present invention may be used in a number of beneficial ways. For example, an isotopically-labeled active agent of a combination of the present invention, *e.g.*, one in which a radioactive isotope such as ^{3}H or ^{14}C has been incorporated, will be useful in drug and/or substrate tissue distribution assays. These radioactive isotopes, *i.e.*, tritium, ^{3}H, and carbon-14, ^{14}C, are especially preferred for their ease of preparation and eminent detectability. Incorporation of heavier isotopes, *e.g.*, deuterium, ^{2}H, into an active agent of a combination of the present invention will provide therapeutic advantages based on the greater metabolic stability of the isotopically-labeled compound. Greater metabolic stability translates directly into increased *in vivo* half-life or reduced dosage requirements, which under most circumstances would constitute a preferred embodiment of the present invention. An isotopically-labeled active agent of a combination of the present invention can usually be prepared by carrying out the procedures disclosed in the Synthesis

Schemes and related description, Examples, and Preparations herein, substituting a readily available isotopically-labeled reagent for its corresponding non-isotopically-labeled reagent.

Deuterium, ^2H, can also be incorporated into an active agent of a combination of the present invention for the purpose of manipulating the oxidative metabolism of the active agent by way of the primary kinetic isotope effect. The primary kinetic isotope effect is a change of rate for a chemical reaction that results from substitution of isotopic nuclei, which in turn is caused by the change in ground state energies required for covalent bond formation subsequent to the isotopic substitution. Substitution of a heavier isotope will usually result in a lowering of the ground state energy for a chemical bond, thereby causing a reduction in rate for a rate-limiting bond breaking step. If the bond-breaking event occurs on or near a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. By way of illustration, when deuterium is bound to a carbon atom at a non-exchangeable site, rate differences of k_M/k_D = 2-7 are typical. This difference in rate, applied successfully to an oxidatively labile active agent of a combination of the present invention, can dramatically affect the profile of the active agent *in vivo* and result in improved pharmacokinetic properties.

In discovering and developing therapeutic agents, the skilled artisan seeks to optimize pharmacokinetic parameters while retaining desirable *in vitro* properties. It is a reasonable surmise that many compounds with poor pharmacokinetic profiles suffer from a lability to oxidative metabolism. *In vitro* liver microsomal assays now available provide valuable information about the course of this oxidative metabolism, which in turn permits the rational design of deuterated active agents used in a combination of the present invention with improved stability through resistance to such oxidative metabolism. Significant improvements in the pharmacokinetic profiles of an active agent of a combination of the present invention are thereby obtained, and can be expressed quantitatively in terms of increases in *in vivo* half-life (t/2), concentration at maximum therapeutic effect (C_{max}), area under the dose response curve (AUC), and F; and in terms of decreases in clearance, dose, and cost-of-goods.

By way of illustration of the above, an active agent of a combination of the present invention which has multiple potential sites for oxidative metabolism, *e.g.*, benzylic hydrogen atoms and hydrogen atoms α to a nitrogen atom, is prepared as a series of analogs in which various combinations of hydrogen atoms are replaced by deuterium atoms so that some, most or all of the hydrogen atoms are replaced with deuterium atoms. Half-life determinations provide an expedient and accurate determination of the extent of improvement in resistance to oxidative metabolism. In this manner it is determined that the half-life of the parent compound can be extended by as much as 100% as the result of such deuterium-for-hydrogen substitution.

Deuterium-for-hydrogen substitution in an active agent of a combination of the present invention can also be used to achieve a favorable alteration in the metabolite profile of the parent compound as a way of diminishing or eliminating unwanted toxic metabolites. For example, where a toxic metabolite arises through an oxidative carbon-hydrogen, C—H, bond scission, the deuterated analog is reasonably expected to greatly diminish or eliminate production of the unwanted metabolite, even in the case where the particular oxidation is not a rate-determining step.

Further information concerning the state of the art with respect to deuterium-for-hydrogen substitution may be found, *e.g.*, in Hanzlik *et al.*, *J. Org. Chem.* **55** 3992-3997, 1990; Reider *et al.*, *J. Org. Chem.* **52** 3326-3334, 1987; Foster, *Adv. Drug Res.* **14** 1-40, 1985; Gillette *et al.*, *Biochemistry* **33**(10) 2927-2937, 1994; and Jarman *et al.*, *Carcinogenesis* **16**(4) 683-688, 1993.

Detailed Description of the Invention

Therapeutic Applications and Clinical Endpoints

The description which follows concerns the therapeutic applications to which the combinations of compounds of the present invention may be put, and where applicable an explanation of the clinical endpoints associated with such therapeutic applications. There is also set forth a disclosure of various *in vitro* assays and animal model experiments, which are capable of providing data sufficient to define and demonstrate the therapeutic utility of the combinations of compounds of the present invention.

The therapeutic utility of the combinations of compounds of the present invention is applicable to a patient or subject afflicted with a disease or condition as herein set forth and therefore in need of such treatment. The beneficial results are therapeutic whether administered to animals or humans. As used herein the terms "animal" and "animals" is used merely for the purpose of pointing out human beings as opposed to other members of the animal kingdom. The combinations of compounds of the present invention have therapeutic applicability in the treatment of mammals, and in particular of humans. All of the major subdivisions of the class of mammals (*Mammalia*) are included within the scope of the present invention with regard to being recipients of therapeutic treatment as described herein. Mammals have value as pets to humans and are therefore likely to be subjects of treatment. This applies especially to the canine and feline groups of mammals. Other mammals are valued as domesticated animals and their treatment in accordance with the present invention is likely in view of the adverse economic impact of not treating the diseases and conditions described herein. This applies especially to the equine, bovine, porcine, and ovine groups of mammals.

The types of diseases that may be treated using the novel combinations of compounds of the present invention include but are not limited to asthma; chronic or acute bronchoconstriction; bronchitis; chronic bronchitis; small airways obstruction; emphysema; chronic obstructive pulmonary disease (COPD); COPD that has chronic bronchitis, pulmonary emphysema or dyspnea associated therewith; COPD that is characterized by irreversible, progressive airways obstruction; adult respiratory distress syndrome (ARDS); exacerbation of airways hyper-

reactivity consequent to drug therapy; pneumoconiosis; acute bronchitis; acute laryngotracheal bronchitis; arachidic bronchitis; catarrhal bronchitis; croupus bronchitis; dry bronchitis; infectious asthmatic bronchitis; productive bronchitis; staphylococcus or streptococcal bronchitis; vesicular bronchitis; cylindric bronchiectasis; sacculated bronchiectasis; fusiform bronchiectasis; capillary bronchiectasis; cystic bronchiectasis; dry bronchiectasis; follicular bronchiectasis; seasonal allergic rhinitis; perennial allergic rhinitis; purulent or nonpurulent sinusitis; acute or chronic sinusitis; ethmoid, frontal, maxillary, or sphenoid sinusitis; eosinophilia; pulmonary infiltration eosinophilia; Loffler's syndrome; chronic eosinophilic pneumonia; tropical pulmonary eosinophilia; bronchopneumonic aspergillosis; aspergilloma; granulomas containing eosinophils; allergic granulomatous angiitis or Churg-Strauss syndrome; sarcoidosis; alveolitis; chronic hypersensitivity pneumonitis; diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis; and idiopathic pulmonary fibrosis.

Asthma

One of the most important respiratory diseases treatable with the combinations of therapeutic agents of the present invention is asthma, a chronic, increasingly common disorder encountered worldwide and characterized by intermittent reversible airway obstruction, airway hyper-responsiveness and inflammation. The cause of asthma has yet to be determined, but the most common pathological expression of asthma is inflammation of the airways, which may be significant even in the airways of patients with mild asthma. This inflammation drives reflex airway events resulting in plasma protein extravasation, dyspnea, and bronchoconstriction. Based on bronchial biopsy and lavage studies, it has been clearly shown that asthma involves infiltration by mast cells, eosinophils, and T-lymphocytes into a patient's airways. Bronchoalveolar lavage (BAL) in atopic asthmatics shows activation of interleukin (IL)-3, IL-4, IL-5 and granulocyte/macrophage-colony stimulating factor (GM-CSF) that suggests the presence of a T-helper 2 (Th-2)-like T-cell population.

The combinations of therapeutic agents of the present invention are useful in the treatment of atopic and non-atopic asthma. The term "atopy" refers to a genetic predisposition toward the development of type I (immediate) hypersensitivity reactions against common environmental antigens. The most common clinical manifestation is allergic rhinitis, while bronchial asthma,

atopic dermatitis, and food allergy occur less frequently. Accordingly, the expression "atopic asthma" as used herein is intended to be synonymous with "allergic asthma", *i.e.*, bronchial asthma which is an allergic manifestation in a sensitized person. The term "non-atopic asthma" as used herein is intended to refer to all other asthmas, especially essential or "true" asthma, which is provoked by a variety of factors, including vigorous exercise, irritant particles, psychologic stresses, etc.

The use of the combinations of therapeutic agents of the present invention to treat atopic asthma or non-atopic asthma, COPD or other chronic airways diseases may be established and demonstrated by use of a number of different models of known in the art of inhibition reflex events in the airway including plasma extravasation and bronchospasmolytic models described below.

Bronchodilator Activity: cAMP is involved not only in smooth muscle relaxation, but also exerts an overall inhibitory influence on airway smooth muscle proliferation, both of which may result from A_{2A} receptors by a component of the invention. Airway smooth muscle hypertrophy and hyperplasia can be modulated by cAMP, and these conditions are common morphological features of chronic asthma.

Relaxation of Human Bronchus: Samples of human lungs dissected during surgery for cancer are obtained within 3 days after removal. Small bronchi (inner diameter ≈ 2 to 5 mm) are excised, cut into segments and placed in 2 mL liquid nitrogen storage ampoules filled with fetal calf serum (FCS) containing 1.8 M dimethylsulfoxide (DMSO) and 0.1M sucrose as cryoprotecting agents. The ampoules are placed in a polystyrol box (11 x 11 x 22 cm) and slowly frozen at a mean cooling rate of about 0.6°C/m in a freezer maintained at -70°C. After 3-15h the ampoules are transferred into liquid nitrogen (-196°C) where they are stored until use. Before use the tissues are exposed for 30-60 minutes to -70°C before being thawed within 2.5m by placing the ampoules in a 37°C water bath. Thereafter the bronchial segments are rinsed by placing them in a dish containing Krebs-Henseleit solution (μM: NaCl 118, KCl 4.7, $MgSO_4$ 1.2, $CaCl_2$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11, EDTA 0.03) at 37°C, cut into rings and suspended in 10 mL organ baths for isometric tension recording under a preload of

about 1g. Further increases in tension are induced *via* the application of field stimulation, which is known to induce activation of nerves in the airway sample and generate tension *via* release of acetylcholine and other neurally derived mediators. Concentration-response curves are produced by cumulative additions, each concentration being added when the maximum effect has been produced by the previous concentration. Papaverine (300 μM) is added at the end of the concentration response curve to induce complete relaxation of the bronchial rings. This effect is taken as 100% relaxation.

In the above test model the combinations of therapeutic agents of the present invention produce concentration-related relaxation of human bronchus ring preparations at concentrations in the range of from 0.001 μM to 1.0 μM with preferred embodiments being active at concentrations in the range of from 5.0 nM to 50 nM.

Suppression of Capsaicin-induced Bronchoconstriction: Male Dunkin-Hartley guinea- pigs (400-800g) having free access to food and water prior to the experiment, are anaesthetized with sodium phenobarbital (100 mg/kg *i.p.* [intraperitoneal]). Animals, maintained at 37°C with a heated pad, controlled by a rectal thermometer, are ventilated via a tracheal cannula (about 8 mL/kg, 1 Hz) with a mixture of air and oxygen (45:55 v/v). Ventilation is monitored at the trachea by a pneumotachograph connected to a differential pressure transducer in line with the respiratory pump. Pressure changes within the thorax are monitored directly *via* an intrathoracic cannula, using a differential pressure transducer so that the pressure difference between the trachea and thorax can be measured and displayed. From these measurements of air-flow and transpulmonary pressure, both airway resistance (R_1 $cmH_2O/l/s$) and compliance (Cd_{dyn}) are calculated with a digital electronic respiratory analyzer for each respiratory cycle. Blood pressure and heart rate are recorded from the carotid artery using a pressure transducer.

When values for basal resistance and compliance are stable, an acute episode of bronchoconstriction is induced by an intravenous bolus of capsaicin. Capsaicin is dissolved in 100% ethanol and diluted with phosphate buffered saline. Test combinations of therapeutic agents of the present invention are administered when the response to capsaicin is stable, which is calculated to be after 2-3 such administrations at 10 minute intervals. Reversal of

bronchoconstriction is assessed over 1-8 hours following either intratracheal or intraduodenal instillation or intravenous bolus injection. Bronchospasmolytic activity is expressed as a % inhibition of the initial, maximal resistance (R_D) following the infusion of capsaicin. ED_{50} values represent the dose which causes a 50% reduction of the increase in resistance induced by capsaicin. Duration of action is defined as the time in minutes where bronchoconstriction is reduced by 50% or more. Effects on blood pressure (BP) and heart rate (HR) are characterized by ED_{20} values; *i.e.*, the doses which reduce BP or HR by 20% measured 5m after administration.

In the above test model the combinations of therapeutic agents of the present invention exhibit bronchodilator activity at dosages in the range of from 0.001 to 0.1 mg/kg *i.v.* or 0.1 to 5.0 mg/kg *i.d.* or 0.0001 to 0.01 mg/kg *i.t.* [intratracheal]. Further, the combination delivered *i.t.* exhibits an at least additive inhibitory effect on bronchospasm, with each component alone being able to inhibit more than 50% of the observed control response.

Allergic Guinea Pig Assay: A test for evaluating the therapeutic impact of the 32 combinations of therapeutic agents of the present invention on the symptom of dyspnea and bronchospasm, *i.e.*, difficult or labored breathing and increased lung resistance, and on the symptom of inflammation, *i.e.* lung neutrophilia and eosinophilia, utilizes Dunkin-Hartley guinea-pigs (400-600 g body weight).

The egg albumin (EA), grade V, crystallized and lyophilized, aluminum hydroxide, and mepyramine maleate used in this test are commercially available. The challenge and subsequent respiratory readings are carried out in a clear plastic box with internal dimensions of 10x6x4 inches. The head and body sections of the box are separable. In use, the two sections are held firmly together by clamps, and an airtight seal between the chambers is maintained by means of a soft rubber gasket. Through the center of the head end of the chamber a nebulizer is inserted *via* an airtight seal and each end of the box also has an outlet. A pneumotachograph is inserted into one end of the box and is coupled to a volumetric pressure transducer which is then connected to a dynograph through appropriate couplers. While aerosolizing the antigen, the outlets are open and the pneumotachograph is isolated from

the chamber. The outlets are then closed and the pneumotachograph and the chamber are connected during the recording of the respiratory patterns. For challenge, 2 mL of a 3% solution of antigen in saline is placed in each nebulizer and the aerosol is generated with air from a small diaphragm pump operating at 10 psi and a flow rate of 8 l/m.

Guinea pigs are sensitized by injecting subcutaneously and *i.p.* 1 mL of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. They are used between days 12 and 24 post-sensitization. In order to eliminate the histamine component of the response, guinea pigs are pretreated *i.p.* 30 minutes prior to aerosol challenge with 2.0 mg/kg of mepyramine. Guinea pigs are then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then respiratory profiles are recorded for a further 30 minutes. Subsequently, lung inflammation is determined post mortem over a period of 1-48 hours. The duration of continuous dyspnea is measured from the respiratory recordings.

Test combinations of therapeutic agents of the present invention are generally administered *i.t.* or by aerosol 0.5-4 hours prior to challenge. The combinations of compounds are either dissolved in saline or biocompatable solvents. The activity of the compounds are determined on the basis of their ability to decrease the magnitude and duration of symptoms of dyspnea and bronchospasm and/or the magnitude of lung inflammation in comparison to a group of vehicle-treated controls. Tests of the combinations of therapeutic agents of the present invention are evaluated over a series of doses and an ED_{50} is derived that is defined as the dose (mg/kg) which will inhibit the duration of symptoms by 50%.

Pulmonary Mechanics in Trained, Conscious Squirrel Monkeys: The ability of the combinations of therapeutic agents of the present invention to inhibit *Ascaris* antigen induced changes in the respiratory parameters, *e.g.*, airway resistance, of squirrel monkey test subjects is evaluated in this method. This test procedure involves placing trained squirrel monkeys in chairs in aerosol exposure chambers. For control purposes, pulmonary mechanics measurements of respiratory parameters are recorded for a period of about 30m to establish each monkey's normal control values for that day. For oral administration, combinations of

compounds of the present invention are dissolved or suspended in a 1% methocel solution (methylcellulose, 65HG, 400 cps) and given in a volume of 1 mL/kg of body weight.

Following challenge, each minute of data is calculated as a percent change from control values for each respiratory parameter including airway resistance (R_L) and dynamic compliance (C_{dyn}). The results for each test compound are subsequently obtained for a minimum period of 60m post-challenge, which are then compared to previously obtained historical baseline control values for the particular monkey involved. Further, the overall values for 60m post-challenge for each monkey, *i.e.*, historical baseline values and test values, are averaged separately and are used to calculate the overall percent inhibition of *Ascaris* antigen response by the test compound. For statistical analysis of the results, the paired t-test is used.

Prevention of Induced Bronchoconstriction in Allergic Sheep: A procedure for testing the therapeutic activity of the combinations of therapeutic agents of the present invention in preventing bronchoconstriction is described below. It is based on the discovery of a certain breed of allergic sheep with a known sensitivity to a specific antigen, *Ascaris suum*, that responds to inhalation challenge with acute as well as late bronchial responses. The progress of both the acute and the late bronchial responses over time approximates the time course observed in humans with asthma; moreover, the pharmacological modification of both the acute and late responses is similar to that found in man. The responses of these sheep to the antigen challenge is observed for the most part in their large airways, which makes it possible to monitor the effects as changes in lung resistance, *i.e.*, specific lung resistance.

Adult sheep with a mean weight of 35 kg (range: 18-50 kg) are used. All animals used meet two criteria: 1) they have a natural cutaneous reaction to 1:1000 or 1:10000 dilutions of *Ascaris suum* extract, and 2) they have previously responded to inhalation challenge with *Ascaris suum* with both an acute bronchoconstriction and a late bronchial obstruction. See Abraham *et al.*, *Am. Rev. Resp. Dis.* **128** 839-844, 1983.

The unsedated sheep are restrained in a cart in the prone position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine solution, a balloon catheter is

advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube through the other nostril using a flexible fiberoptic bronchoscope as a guide. Pleural pressure is estimated with the esophageal balloon catheter (filled with 1 mL of air), which is positioned such that inspiration produces a negative pressure deflection with clearly discernible cardiogenic oscillations. Lateral pressure in the trachea is measured with a sidehole catheter (inner dimensions: 2.5 mm) advanced through and positioned distal to the tip of the nasotracheal tube. Transpulmonary pressure, *i.e.*, the difference between tracheal pressure and pleural pressure, is measured with a differential pressure transducer. Testing of the pressure transducer catheter system reveals no phase shift between pressure and flow to a frequency of 9 Hz. For the measurement of pulmonary resistance (R_L), the maximal end of the nasotracheal tube is connected to a pneumotachograph. The signals of flow and transpulmonary pressure are recorded on an oscilloscope which is linked to a computer for on-line calculation of R_L from transpulmonary pressure, respiratory volume obtained by integration, and flow. Analysis of 10-15 breaths is used for the determination of R_L. Thoracic gas volume (V_{tg}) is measured in a body plethysmograph, to obtain pulmonary resistance ($SR_L = R_L \cdot V_{tg}$).

Aerosols of *Ascaris suum* extract (1:20) are generated using a disposable medical nebulizer which produces an aerosol with a mass median aerodynamic diameter of 6.2 □m (geometric standard deviation, 2.1) as determined by an electric size analyzer. The output from the nebulizer is directed into a plastic T-piece, one end of which is attached to the nasotracheal tube, and the other end of which is connected to the inspiratory part of a conventional respirator. The aerosol is delivered at a total volume of 500 mL at a rate of 20 mL per minute. Thus, each sheep receives an equivalent dose of antigen in both placebo and drug trials.

Prior to antigen challenge, baseline measurements of SR_L are obtained, infusion of the test compound is started 1 hour prior to challenge, the measurement of SR_L is repeated, and the sheep then undergoes inhalation challenge with *Ascaris suum* antigen. Measurements of SR_L are obtained immediately after antigen challenge and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, and 8h after antigen challenge. Placebo and drug tests are separated by at least 14 days. In a further study, sheep are given a bolus dose of the test compound followed by an infusion of the test

compound for 0.5-1 hour prior to *Ascaris* challenge and for 8 hours after *Ascaris* challenge as described above. A Kruskal-Wallis one way ANOVA test is used to compare the acute immediate responses to antigen and the peak late response in the controls and the drug treated animals.

Another useful assay, based on the use of primates, is that described in Turner *et al.*, "Characterization of a primate model of asthma using anti-allergy/anti-asthma agents," *Inflammation Research* **45** 239-245, 1996.

Anti-inflammatory Activity: The anti-inflammatory activity of the combinations of therapeutic agents of the present invention is demonstrated by the inhibition of eosinophil activation. In this assay blood samples (50 mL) are collected from non-atopic volunteers with eosinophil numbers ranging between 0.06 and 0.47 x 10^9 L^{-1}. Venous blood is collected into centrifuge tubes containing 5 mL trisodium citrate (3.8%, pH 7.4).

The anticoagulated blood is diluted (1:1, v:v) with phosphate-buffered saline (PBS, containing neither calcium nor magnesium) and is layered onto 15 mL isotonic Percoll (density 1.082 - 1.085 g/mL, pH 7.4), in a 50 mL centrifuge tube. Following centrifugation (30 minutes, 1000 x g, 20°C), mononuclear cells at the plasma/Percoll interface are aspirated carefully and discarded.

The neutrophil/eosinophil/erythrocyte pellet (*ca.* 5 mL by volume) is gently resuspended in 35 mL of isotonic ammonium chloride solution (NH_4Cl, 155 mM; $KHCO_3$, 10 mM; EDTA. 0.1 mM; 0-4°C). After 15 minutes, cells are washed twice (10 min, 400 x g, 4°C) in PBS containing fetal calf serum (2%, FCS).

A magnetic cell separation system is used to separate eosinophils and neutrophils. This system is able to separate cells in suspension according to surface markers, and comprises a permanent magnet, into which is placed a column that includes a magnetizable steel matrix. Prior to use, the column is equilibrated with PBS/FCS for 1 hour and then flushed with ice-cold PBS/FCS

on a retrograde basis *via* a 20 mL syringe. A 21G hypodermic needle is attached to the base of the column and 1-2 mL of ice cold buffer are allowed to efflux through the needle.

Following centrifugation of granulocytes, supernatant is aspirated and cells are gently resuspended with 100µl magnetic particles (anti-CD16 monoclonal antibody, conjugated to superparamagnetic particles). The eosinophil/neutrophil/anti-CD16 magnetic particle mixture is incubated on ice for 40 minutes and then diluted to 5 mL with ice-cold PBS/FCS. The cell suspension is slowly introduced into the top of the column and the tap is opened to allow the cells to move slowly into the steel matrix. The column is then washed with PBS/FCS (35 mL), which is carefully added to the top of the column so as not to disturb the magnetically labeled neutrophils already trapped in the steel matrix. Non-labeled eosinophils are collected in a 50 mL centrifuge tube and washed (10 minutes, 400 x g, 4°C). The resulting pellet is resuspended in 5 mL Hank's balanced salt solution (HBSS) so that cell numbers and purity can be assessed prior to use. The separation column is removed from the magnet and the neutrophil fraction is eluted. The column is then washed with PBS (50 mL) and ethanol (absolute), and stored at 4°C.

Total cells are counted with a micro cell counter. One drop of lysogenic solution is added to the sample, which after 30s is recounted to assess contamination with erythrocytes. Cytospin smears are prepared on a Shandon Cytospin 2 cytospinner (100 µL samples, 3 minutes, 500 rpm). These preparations are stained and differential cell counts are determined by light microscopy, examining at least 500 cells. Cell viability is assessed by exclusion of trypan blue.

Eosinophils or neutrophils are diluted in HBSS and pipetted into 96 well microtiter plates (MTP) at 1-10 x 10^3 cells/well. Each well contains a 200 µL sample comprising: 100 µL eosinophil suspension; 50 µL HBSS; 10 µL lucigenin; 20 µL activation stimulus; and 20 µL test compound.

The samples are incubated with test compound or vehicle for 10m prior to addition of an activation stimulus fMLP (10 µM) or C5a (1-100 nM) dissolved in dimethylsulfoxide and

thereafter diluted in buffer, such that the highest solvent concentration used is 1% (at 100 μM test compound). MTPs are agitated to facilitate mixing of the cells and medium, and the MTP is placed into a luminometer. Total chemiluminescence and the temporal profile of each well is measured simultaneously over 20m and the results expressed as arbitrary units, or as a percentage of fMLP-induced chemiluminescence in the absence of test compound. Results are fitted to the Hill equation and IC_{50} values are calculated automatically.

The combinations of therapeutic agents of the present invention are active in the above test method at concentrations in the range of from 0.0001 μM to 0.5 μM, with preferred embodiments being active at concentrations in the range of from 0.5 nM to 100 nM.

From the above it may be seen that the combinations of therapeutic agents of the present invention are useful for the treatment of inflammatory or obstructive airways diseases or other conditions involving airways obstruction. In particular they are useful for the treatment of bronchial asthma.

In view of their anti-inflammatory activity and their influence on airways hyper-reactivity, the combinations of therapeutic agents of the present invention are useful for the treatment, in particular prophylactic treatment, of obstructive or inflammatory airways diseases. Thus, by continued and regular administration over prolonged periods of time the combinations of compounds of the present invention are useful in providing advance protection against the recurrence of bronchoconstriction or other symptomatic attack consequential to obstructive or inflammatory airways diseases. The combinations of compounds of the present invention are also useful for the control, amelioration or reversal of the basal status of such diseases.

Having regard to their bronchodilator activity the combinations of therapeutic agents of the present invention are useful as bronchodilators, *e.g.*, in the treatment of chronic or acute bronchoconstriction, and for the symptomatic treatment of obstructive or inflammatory airways diseases.

The words "treatment" and "treating" as used throughout the present specification and claims in relation to obstructive or inflammatory airways diseases are to be understood, accordingly, as embracing both prophylactic and symptomatic modes of therapy.

In light of the above description, it may be seen that the present invention also relates to a method for the treatment of airways hyper-reactivity in mammals; to a method of effecting bronchodilation in mammals; and in particular, to a method of treating obstructive or inflammatory airways diseases, especially asthma, in a mammal subject in need thereof, which method comprises administering to the subject mammal an effective amount of a combination of therapeutic agents of the present invention.

Obstructive or inflammatory airways diseases to which the present invention applies include asthma; pneumoconiosis; chronic eosinophilic pneumonia; chronic obstructive airways or pulmonary disease (COAD or COPD); and adult respiratory distress syndrome (ARDS), as well as exacerbation of airways hyper-reactivity consequent to other drug therapy, *e.g.*, aspirin or β-agonist therapy.

The combinations of therapeutic agents of the present invention are useful in the treatment of asthma of whatever type, etiology, or pathogenesis; including intrinsic asthma attributed to pathophysiologic disturbances, extrinsic asthma caused by some factor in the environment, and essential asthma of unknown or inapparent cause. The combinations of therapeutic agents of the present invention are useful in the treatment of allergic (atopic/bronchial/IgE-mediated) asthma; and they are useful as well in the treatment of non-atopic asthma, including *e.g.* bronchitic, emphysematous, exercise-induced, and occupational asthma; infective asthma that is a sequela to microbial, especially bacterial, fungal, protozoal, or viral infection; and other non-allergic asthmas, *e.g.*, incipient asthma (wheezy infant syndrome).

The combinations of therapeutic agents of the present invention are further useful in the treatment of pneumoconiosis of whatever type, etiology, or pathogenesis; including, *e.g.*, aluminosis (bauxite workers' disease); anthracosis (miners' asthma); asbestosis (steam-fitters' asthma); chalicosis (flint disease); ptilosis caused by inhaling the dust from ostrich feathers;

siderosis caused by the inhalation of iron particles; silicosis (grinders' disease); byssinosis (cotton-dust asthma); and talc pneumoconiosis.

Chronic Obstructive Pulmonary Disease (COPD)

The combinations of therapeutic agents of the present invention are still further useful in the treatment of COPD or COAD including chronic bronchitis, pulmonary emphysema or dyspnea associated therewith. COPD is characterized by irreversible, progressive airways obstruction. Chronic bronchitis is associated with hyperplasia and hypertrophy of the mucus secreting glands of the submucosa in the large cartilaginous airways. Goblet cell hyperplasia, mucosal and submucosal inflammatory cell infiltration, edema, fibrosis, mucus plugs and increased smooth muscle are all found in the terminal and respiratory bronchioles. The small airways are known to be a major site of airway obstruction. Emphysema is characterized by destruction of the alveolar wall and loss of lung elasticity. A number of risk factors have also been identified as linked to the incidence of COPD. The link between tobacco smoking and COPD is well established. Other risk factors include exposure to coal dust and various genetic factors. See Sandford *et al.*, "Genetic risk factors for chronic obstructive pulmonary disease," *Eur. Respir. J.* **10** 1380-1391, 1997. The incidence of COPD is increasing and it represents a significant economic burden on the populations of the industrialized nations. COPD also presents itself clinically with a wide range of variation from simple chronic bronchitis without disability to patients in a severely disabled state with chronic respiratory failure.

COPD is characterized by inflammation of the airways, as is the case with asthma, but the inflammatory cells that have been found in the bronchoalveolar lavage fluid and sputum of patients neutrophils rather than eosinophils. Elevated levels of inflammatory mediators are also found in COPD patients, including IL-8, LTB_4, and TNFα, and the surface epithelium and sub-epithelium of the bronchi of such patients has been found to be infiltrated by T-lymphocytes and macrophages. Symptomatic relief for COPD patients can be provided by the use of β-agonist and anticholinergic bronchodilators, but the progress of the disease remains unaltered. COPD has been treated using theophylline, but without much success, even though it reduces neutrophil counts in the sputum of COPD patients. Steroids have also failed to hold

out much promise as satisfactory treatment agents in COPD as they are relatively ineffective as anti-inflammatory agents.

Accordingly, the use of the combinations of therapeutic agents of the present invention to treat COPD and its related and included obstructed airways diseases, represents a significant advance in the art. The present invention is not limited to any particular mode of action or any hypothesis as to the way in which the desired therapeutic objectives have been obtained by utilizing the combinations of therapeutic agents of the present invention.

Bronchitis and Bronchiectasis

In accordance with the particular and diverse inhibitory activities described above that are possessed by the combinations of therapeutic agents of the present invention, they are useful in the treatment of bronchitis of whatever type, etiology, or pathogenesis, including, *e.g.*, acute bronchitis which has a short but severe course and is caused by exposure to cold, breathing of irritant substances, or an acute infection; acute laryngotracheal bronchitis which is a form of nondiphtheritic croup; arachidic bronchitis which is caused by the presence of a peanut kernel in a bronchus; catarrhal bronchitis which is a form of acute bronchitis with a profuse mucopurulent discharge; chronic bronchitis which is a long-continued form of bronchitis with a more or less marked tendency to recurrence after stages of quiescence, due to repeated attacks of acute bronchitis or chronic general diseases, characterized by attacks of coughing, by expectoration either scanty or profuse, and by secondary changes in the lung tissue; croupus bronchitis which is characterized by violent cough and paroxysms of dyspnea; dry bronchitis which is characterized by a scanty secretion of tough sputum; infectious asthmatic bronchitis which is a syndrome marked by the development of symptoms of bronchospasm following respiratory tract infections in persons with asthma; productive bronchitis which is bronchitis associated with a productive cough; staphylococcus or streptococcal bronchitis which are caused by staphylococci or streptococci; and vesicular bronchitis in which the inflammation extends into the alveoli, which are sometimes visible under the pleura as whitish-yellow granulations like millet seeds.

Bronchiectasis is a chronic dilatation of the bronchi marked by fetid breath and paroxysmal coughing with the expectoration of mucopurulent matter. It may affect the tube uniformly, in which case it is referred to as cylindric bronchiectasis, or it may occur in irregular pockets, in which case it is called sacculated bronchiectasis. When the dilated bronchial tubes have terminal bulbous enlargements, the term fusiform bronchiectasis is used. In those cases where the condition of dilatation extends to the bronchioles, it is referred to as capillary bronchiectasis. If the dilatation of the bronchi is spherical in shape, the condition is referred to as cystic bronchiectasis. Dry bronchiectasis occurs where the infection involved is episodic and it may be accompanied by hemoptysis, the expectoration of blood or of blood-stained sputum. During quiescent periods of dry bronchiectasis, the coughing which occurs is nonproductive. Follicular bronchiectasis is a type of bronchiectasis in which the lymphoid tissue in the affected regions becomes greatly enlarged, and by projection into the bronchial lumen, may seriously distort and partially obstruct the bronchus. Accordingly, the combinations of therapeutic agents of the present invention are useful in the beneficial treatment of the various above-described types of bronchiectasis as a direct result of their inhibition of PDE4 isozymes.

The utility of the combinations of therapeutic agents of the present invention as bronchodilators or bronchospasmolytic agents for treating bronchial asthma, chronic bronchitis and related diseases and disorder described herein, is demonstrable through the use of a number of different *in vivo* animal models known in the art, including those described in the paragraphs below.

Bronchospasmolytic Activity *In Vitro*: The ability of the combinations of therapeutic agents of the present invention to cause relaxation of guinea-pig tracheal smooth muscle is demonstrated in the following test procedure. Guinea pigs (350-500 g) are killed with sodium pentothal (100 mg/kg i.p.). The trachea is dissected and a section 2-3 cm in length is excised. The trachea is transected in the transverse plane at alternate cartilage plates so as to give rings of tissue 3-5 mm in depth. The proximal and distal rings are discarded. Individual rings are mounted vertically on stainless steel supports, one of which is fixed at the base of an organ bath, while the other is attached to an isometric transducer. The rings are bathed in Krebs solution

(composition μM: $NaHCO_3$ 25; NaCl 113; KCl 4.7; $MgSO_4 \cdot 7H_2O$ 1.2; KH_2PO_4 1.2; $CaCl_2$ 2.5; glucose 11.7) at 37°C and gassed with O_2/CO_2 (95:5, v/v). Rings prepared in this manner, preloaded to 1 g, generate spontaneous tone and, after a period of equilibration (45-60m), relax consistently on addition of spasmolytic drugs. To ascertain spasmolytic activity, test combinations of therapeutic agents of the present invention are dissolved in physiological saline and added in increasing quantities to the organ bath at 5m intervals to provide a cumulative concentration-effect curve.

In the above test model, combinations of therapeutic agents of the present invention produce concentration-related relaxation of guinea pig tracheal ring preparations at concentrations in the range of from 0.001 to 1.0 μM.

Suppression of Airways Hyper-reactivity in PAF-treated Animals: Guinea pigs are anesthetized and prepared for recording of lung function as described under "Suppression of bombesin-induced bronchoconstriction" further above. Intravenous injection of low dose histamine (1.0-1.8 μg/kg) establishes airways sensitivity to spasmogens. Following infusion of PAF (platelet activating factor) over 1 hour (total dose = 600 ng/kg), injection of low dose bombesin 20m after cessation of infusion reveals development of airways hyper-reactivity, which is expressed as the paired difference between the maximal response amplitude before and after PAF exposure. Upon administration of the combinations of therapeutic agents of the present invention by infusion during PAF exposure at dosages in the range of from 0.01 to 0.1 mg/kg, suppression of PAF-induced hyper-reactivity is obtained.

Allergic and Other Types of Rhinitis; Sinusitis

Allergic rhinitis is characterized by nasal obstruction, itching, watery rhinorrhea, sneezing and occasional anosmia. Allergic rhinitis is divided into two disease categories, seasonal and perennial, in which the former is attributed to pollen or outdoor mold spores, while the latter is attributed to common allergens such as house dust mites, animal danders, and mold spores. Allergic rhinitis generally exhibits an early phase response and a late phase response. The early phase response is associated with mast cell degranulation, while the late phase response is characterized by infiltration of eosinophils, basophils, monocytes, and T-lymphocytes. A

variety of inflammatory mediators is also released by these cells, all of which may contribute to the inflammation exhibited in the late phase response.

A particularly prevalent form of seasonal allergic rhinitis is hay fever, which is marked by acute conjunctivitis with lacrimation and itching, swelling of the nasal mucosa, nasal catarrh, sudden attacks of sneezing, and often with asthmatic symptoms. The combinations of compounds of the present invention are especially useful in the beneficial treatment of hay fever.

Other types of rhinitis for which the combinations of therapeutic agents of the present invention may be used as therapeutic agents include acute catarrhal rhinitis which is a cold in the head involving acute congestion of the mucous membrane of the nose, marked by dryness and followed by increased mucous secretion from the membrane, impeded respiration through the nose, and some pain; atrophic rhinitis which is a chronic form marked by wasting of the mucous membrane and the glands; purulent rhinitis which is chronic rhinitis with the formation of pus; and vasomotor rhinitis which is a non-allergic rhinitis in which transient changes in vascular tone and permeability with the same symptoms as allergic rhinitis, are brought on by such stimuli as mild chilling, fatigue, anger, and anxiety.

There is a recognized link between allergic rhinitis and asthma. Allergic rhinitis is a frequent accompaniment to asthma, and it has been demonstrated that treating allergic rhinitis will improve asthma. Epidemiologic data has also been used to show a link between severe rhinitis and more severe asthma. For example, the compound D-22888, under preclinical development for the treatment of allergic rhinitis, has been shown to exhibit a strong antiallergic affect and to inhibit rhinorrhea in the antigen-challenged pig. See, Marx *et* 30 *al* "D-22888 - a new PDE4 inhibitor for the treatment of allergic rhinitis and other allergic disorders," *J. Allergy Clin. Immunol.* 99 S444, 1997.

Sinusitis is related to rhinitis in terms of anatomical proximity as well as a shared etiology and pathogenesis in some cases. Sinusitis is the inflammation of a sinus and this condition may be purulent or nonpurulent, as well as acute or chronic. Depending upon the sinus where the

inflammation is located, the condition is known as ethmoid, frontal, maxillary, or sphenoid sinusitis. The ethmoidal sinus is one type of paranasal sinus, located in the ethmoid bone. The frontal sinus is one of the paired paranasal sinuses located in the frontal bone. The maxillary sinus is one of the paired paranasal sinuses located in the body of the maxilla. Accordingly, the combinations of therapeutic agents of the present invention are useful in the beneficial treatment of acute or chronic sinusitis, but especially of chronic sinusitis.

Eosinophil-Related Disorders

The ability of the combinations of compounds of the present invention to inhibit eosinophil activation as part of their overall anti-inflammatory activity has been described above. Accordingly, the combinations of compounds of the present invention are useful in the therapeutic treatment of eosinophil-related disorders. Such disorders include eosinophilia, which is the formation and accumulation of an abnormally large number of eosinophils in the blood. The name of the disorder derives from "eosin", a rose-colored stain or dye comprising a bromine derivative of fluorescein which readily stains "eosinophilic leukocytes" in the blood of patients who are thus readily identified. A particular eosinophilic disorder that can be treated in accordance with the present invention is pulmonary infiltration eosinophilia, which is characterized by the infiltration of the pulmonary parenchyma by eosinophils. This disorder includes especially Loffler's syndrome, which is a condition characterized by transient infiltrations of the lungs, accompanied by cough, fever, dyspnea, and eosinophilia.

Other eosinophilic disorders include chronic eosinophilic pneumonia, which is a chronic interstitial lung disease characterized by cough, dyspnea, malaise, fever, night sweats, weight loss, eosinophilia, and a chest film revealing non-segmental, non-migratory infiltrates in the lung periphery; tropical pulmonary eosinophilia, which is a subacute or chronic form of occult filariasis, usually involving *Brugia malayi, Wuchereria bancrofti,* or filariae that infect animals, occurs in the tropics, and is characterized by episodic nocturnal wheezing and coughing, strikingly elevated eosinophilia, and diffuse reticulonodular infiltrations of the lungs; bronchopneumonic aspergillosis, which is an infection of the bronchi and lungs by *Aspergillus* fungi resulting in a diseased condition marked by inflammatory granulomatous lesions in the nasal sinuses and lungs, but also in the skin, ear, orbit, and sometimes in the

bones and meninges, and leading to aspergilloma, the most common type of fungus ball formed by colonization of *Aspergillus* in a bronchus or lung cavity.

The term "granulomatous" means containing granulomas, and the term "granuloma" refers to any small nodular delimited aggregation of mononuclear inflammatory cells or such a collection of modified macrophages resembling epithelial cells, usually surrounded by a rim of lymphocytes, with fibrosis commonly seen around the lesion. Some granulomas contain eosinophils. Granuloma formation represents a chronic inflammatory response initiated by various infectious and noninfectious agents. A number of such granulomatous conditions are treatable using combinations of compounds of the present invention, e.g., allergic granulomatous angiitis, also called Churg-Strauss syndrome, which is a form of systemic necrotizing vasculitis in which there is prominent lung involvement, generally manifested by eosinophilia, granulomatous reactions, and usually severe asthma. A related disorder is polyarteritis nodosa (PAN), which is marked by multiple inflammatory and destructive arterial lesions and is a form of systemic necrotizing vasculitis involving the small and medium-sized arteries with signs and symptoms resulting from infarction and scarring of the affected organ system, in particular the lungs. Other eosinophil-related disorders which may be treated in accordance with the present invention are those affecting the airways which are induced or occasioned by a reaction to a therapeutic agent unrelated to any combinations of compounds of the present invention.

Pharmaceutical Compositions, Formulations, and Delivery Devices

The description which follows concerns the manner in which the combinations of compounds of the present invention, together with other therapeutic agents or non-therapeutic agents where these are desired, are combined with what are for the most part conventional pharmaceutically acceptable carriers to form dosage forms suitable for administration by inhalation to any given patient, as well as appropriate to the disease, disorder, or condition for which any given patient is being treated.

The pharmaceutical compositions of the present invention comprise any one or more of the above-described combinations of compounds of the present invention, or a pharmaceutically

acceptable salt thereof as also above-described, together with a pharmaceutically acceptable carrier in accordance with the properties and expected performance of such carriers for administration by inhalation, which are well-known in the pertinent art.

The amount of active ingredient that may be combined with the carrier materials will vary depending upon the host and disease or condition being treated. It should be understood, however, that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific component compounds employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, and the judgment of the treating physician and the severity of the particular disease being treated.

The above-described component compounds of the present invention may be utilized in the form of acids, esters, or other chemical classes of compounds to which the components described belong. It is also within the scope of the present invention to utilize those component compounds in the form of pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures described in detail above and well known in the art. An active ingredient comprising a component compound of the present invention is often utilized in the form of a salt thereof, especially where the salt form confers on the active ingredient improved pharmacokinetic properties as compared to the free form of the active ingredient or some other salt form of the active ingredient utilized previously. The pharmaceutically acceptable salt form of the active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which it did not previously possess, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body.

Specific preferred salt forms of specific preferred component compounds of the present invention have already been described above. In more general terms, of the pharmaceutical salts recited further above, those which are preferred include, but are not limited to acetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide,

isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate, and tromethamine.

Multiple salts forms are included within the scope of the present invention where a component compound of the present invention contains more than one group capable of forming such pharmaceutically acceptable salts. Examples of typical multiple salt forms include, but are not limited to bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium, and trihydrochloride.

The pharmaceutical compositions of the present invention comprise any one or more of the above-described component compounds of the present invention, or a pharmaceutically acceptable salt thereof as also above-described, together with a pharmaceutically acceptable carrier suitable for administration by inhalation, in accordance with the properties and expected performance of such carriers which are well-known in the pertinent art.

The term "carrier" as used herein includes acceptable diluents, excipients, adjuvants, vehicles, solubilization aids, viscosity modifiers, preservatives and other agents well known to the artisan for providing favorable properties in the final pharmaceutical composition to be administered by inhalation. In order to illustrate such carriers, there follows a brief survey of pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of the present invention, and thereafter a more detailed description of the various types of ingredients. Typical carriers include but are by no means limited to, ion exchange compositions; alumina; aluminum stearate; lecithin; serum proteins, *e.g.*, human serum albumin; phosphates; glycine; sorbic acid; potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids; hydrogenated palm oils; water; salts or electrolytes, *e.g.*, prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts; colloidal silica; magnesium trisilicate; polyvinyl pyrrolidone; cellulose-based substances; *e.g.*, sodium carboxymethylcellulose; polyethylene glycol; polyacrylates; waxes; polyethylene-polyoxypropylene-block polymers; and wool fat.

More particularly, the carriers used in the pharmaceutical compositions of the present invention comprise various classes and species of additives which are members independently selected from the groups consisting essentially of those recited in the following paragraphs.

Acidifying and alkalizing agents are added to obtain a desired or predetermined pH and comprise acidifying agents, *e.g.*, acetic acid, glacial acetic acid, malic acid, and propionic acid. Stronger acids such as hydrochloric acid, nitric acid and sulfuric acid may be used but are less preferred. Alkalizing agents include, *e.g.*, edetol, potassium carbonate, potassium hydroxide, sodium borate, sodium carbonate, and sodium hydroxide. Alkalizing agents which contain active amine groups, such as diethanolamine and trolamine, may also be used.

Aerosol propellants that are required to deliver the pharmaceutical composition as an aerosol under significant pressure are described in more detail further below.

Antimicrobial agents including antibacterial, antifungal and antiprotozoal agents are added where the pharmaceutical composition is topically applied to areas of the skin which are likely to have suffered adverse conditions or sustained abrasions or cuts which expose the skin to infection by bacteria, fungi or protozoa. Antimicrobial agents include such compounds as benzyl alcohol, chlorobutanol, phenylethyl alcohol, phenylmercuric acetate, potassium sorbate, and sorbic acid. Antifungal agents include such compounds as benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, and sodium benzoate.

Antimicrobial preservatives are added to the pharmaceutical compositions of the present invention in order to protect them against the growth of potentially harmful microorganisms, which usually invade the aqueous phase, but in some cases can also grow in the oil phase of a composition. Thus, preservatives with both aqueous and lipid solubility are desirable. Suitable antimicrobial preservatives include, *e.g.*, alkyl esters of *p*-hydroxybenzoic acid, propionate salts, phenoxyethanol, methylparaben sodium, propylparaben sodium, sodium dehydroacetate, benzalkonium chloride, benzethonium chloride, benzyl alcohol, hydantoin derivatives, quaternary ammonium compounds and cationic polymers, imidazolidinyl urea, diazolidinyl urea, and trisodium ethylenediamine tetracetate (EDTA). Preservatives are preferably

employed in amounts ranging from about 0.01% to about 2.0% by weight of the total composition.

Antioxidants are added to protect all of the ingredients of the pharmaceutical composition from damage or degradation by oxidizing agents present in the composition itself or the use environment, *e.g.*, anoxomer, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, potassium metabisulfite, propyl octyl and dodecyl gallate, sodium metabisulfite, sulfur dioxide, and tocopherols.

Buffering agents are used to maintain a desired pH of a composition once established, from the effects of outside agents and shifting equilibria of components of the composition. The buffering may be selected from among those familiar to the artisan skilled in the preparation of pharmaceutical compositions, *e.g.*, calcium acetate, potassium metaphosphate, potassium phosphate monobasic, and tartaric acid.

Chelating agents are used to help maintain the ionic strength of the pharmaceutical composition and bind to and effectively remove destructive compounds and metals, and include, *e.g.*, edetate dipotassium, edetate disodium, and edetic acid.

Dispersing and suspending agents are used as aids for the preparation of stable formulations and include, *e.g.*, poligeenan, povidone, and silicon dioxide.

Emulsifying agents, including emulsifying and stiffening agents and emulsion adjuncts, are used for preparing oil-in-water emulsions when these form the basis of the pharmaceutical compositions of the present invention. Such emulsifying agents include, *e.g.*, non-ionic emulsifiers such as C_{10}-C_{20} fatty alcohols and the fatty alcohols condensed with from 2 to 20 moles of ethylene oxide or propylene oxide, (C_6-C_{12})alkyl phenols condensed with from 2 to 20 moles of ethylene oxide, mono- and di-C_{10}-C_{20} fatty acid esters of ethylene glycol, C_{10}-C_{20} fatty acid monoglyceride, diethylene glycol, polyethylene glycols of MW 200-6000, polypropylene glycols of MW 200-3000, and particularly sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan, hydrophilic wax esters, cetostearyl alcohol, oleyl alcohol,

lanolin alcohols, cholesterol, mono- and di-glycerides, glyceryl monostearate, polyethylene glycol monostearate, mixed mono- and distearic esters of ethylene glycol and polyoxyethylene glycol, propylene glycol monostearate, and hydroxypropyl cellulose. Emulsifying agents which contain active amine groups may also be used and typically include anionic emulsifiers such as fatty acid soaps, *e.g.*, sodium, potassium and triethanolamine soaps of C_{10}-C_{20} fatty acids; alkali metal, ammonium or substituted ammonium (C_{10}-C_{30})alkyl sulfates, (C_{10}-C_{30})alkyl sulfonates, and (C_{10}-C_{50})alkyl ethoxy ether sulfonates. Other suitable emulsifying agents include castor oil and hydrogenated castor oil; lecithin; and polymers of 2-propenoic acid together with polymers of acrylic acid, both cross-linked with allyl ethers of sucrose and/or pentaerythritol, having varying viscosities and identified by product names carbomer 910, 934, 934P, 940, 941, and 1342. Cationic emulsifiers having active amine groups may also be used, including those based on quaternary ammonium, morpholinium and pyridinium compounds. Similarly, amphoteric emulsifiers having active amine groups, such as cocobetaines, lauryl dimethylamine oxide and cocoylimidazoline, may be used. Useful emulsifying and stiffening agents also include cetyl alcohol and sodium stearate; and emulsion adjuncts such as oleic acid, stearic acid, and stearyl alcohol.

Excipients include, *e.g.*, laurocapram and polyethylene glycol monomethyl ether.

Preservatives are used to protect pharmaceutical compositions of the present invention from degradative attack by ambient microorganisms, and include, *e.g.*, benzalkonium chloride, benzethonium chloride, alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, cetylpyridinium chloride, monothioglycerol, phenol, phenoxyethanol, methylparagen, imidazolidinyl urea, sodium dehydroacetate, propylparaben, quaternary ammonium compounds, especially polymers such as polixetonium chloride, potassium benzoate, sodium formaldehyde sulfoxylate, sodium propionate, and thimerosal.

Sequestering agents are used to improve the stability of the pharmaceutical compositions of the present invention and include, *e.g.*, the cyclodextrins which are a family of natural cyclic oligosaccharides capable of forming inclusion complexes with a variety of materials, and are of varying ring sizes, those having 6-, 7- and 8-glucose residues in a ring being commonly

referred to as α-cyclodextrins, β-cyclodextrins, and γ-cyclodextrins, respectively. Suitable cyclodextrins include, *e.g.*, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, δ-cyclodextrin and cationized cyclodextrins.

Solvents which may be used in preparing the pharmaceutical compositions of the present invention include, *e.g.*, acetone, alcohol, amylene hydrate, butyl alcohol, corn oil, cottonseed oil, ethyl acetate, glycerin, hexylene glycol, isopropyl alcohol, isostearyl alcohol, methyl alcohol, methylene chloride, mineral oil, peanut oil, phosphoric acid, polyethylene glycol, polyoxypropylene 15 stearyl ether, propylene glycol, propylene glycol diacetate, sesame oil, and purified water.

Stabilizers which are suitable for use include, *e.g.*, calcium saccharate and thymol.

Sugars are often used to impart a variety of desired characteristics to the pharmaceutical compositions of the present invention and in order to improve the results obtained, and include, *e.g.*, monosaccharides, disaccharides and polysaccharides such as glucose, xylose, fructose, reose, ribose, pentose, arabinose, allose, tallose, altrose, mannose, galactose, lactose, sucrose, erythrose, glyceraldehyde, or any combination thereof.

Surfactants are employed to provide stability for the multi-component pharmaceutical compositions of the present invention, enhance existing properties of those compositions, and bestow desirable new characteristics on the compositions. Surfactants are used as wetting agents, antifoam agents, for reducing the surface tension of water, and as emulsifiers, dispersing agents and penetrants, and include, *e.g.*, lapyrium chloride; laureth 4, *i.e.*, α-dodecyl-ω-hydroxy-poly(oxy-1,2-ethanediyl) or polyethylene glycol monododecyl ether; laureth 9, *i.e.*, a mixture of polyethylene glycol monododecyl ethers averaging about 9 ethylene oxide groups per molecule; monoethanolamine; nonoxynol 4, 9 and 10, *i.e.*, polyethylene glycol mono(*p*-nonylphenyl) ether; nonoxynol 15, *i.e.*, α-(*p*-nonylphenyl)-ω-hydroxypenta-deca(oxyethylene); nonoxynol 30, *i.e.*, α-(*p*-nonylphenyl)-ω-hydroxytriaconta(oxyethylene); poloxalene, *i.e.*, nonionic polymer of the polyethylene-polypropylene glycol type, MW = approx. 3000; poloxamer, referred to in the discussion of ointment bases further above;

polyoxyl 8, 40 and 50 stearate, *i.e.*, poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-; octadecanoate; polyoxyl 10 oleyl ether, *i.e.*, poly(oxy-1,2-ethanediyl), α-[(Z)-9-octadecenyl-ω-hydroxy-; polysorbate 20, *i.e.*, sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl); polysorbate 40, *i.e.*, sorbitan, monohexadecanoate, poly(oxy-1,2-ethanediyl); polysorbate 60, *i.e.*, sorbitan, monooctadecanoate, poly(oxy-1,2-ethanediyl); polysorbate 65, *i.e.*, sorbitan, trioctadecanoate, poly(oxy-1,2-ethanediyl); polysorbate 80, *i.e.*, sorbitan, mono-9-monodecenoate, poly(oxy-1,2-ethanediyl); polysorbate 85, *i.e.*, sorbitan, tri-9-octadecenoate, poly(oxy-1,2-ethanediyl); sodium lauryl sulfate; sorbitan monolaurate; sorbitan monooleate; sorbitan monopalmitate; sorbitan monostearate; sorbitan sesquioleate; sorbitan trioleate; and sorbitan tristearate.

The pharmaceutical compositions of the present invention may be prepared using methodology which is well understood by the artisan of ordinary skill. Where the pharmaceutical compositions of the present invention are simple aqueous and/or other solvent solutions, the various components of the overall composition are brought together in any practical order, which will be dictated largely by considerations of convenience. Those components having reduced water solubility, but sufficient solubility in the same co-solvent with water, may all be dissolved in the co-solvent, after which the co-solvent solution will be added to the water portion of the carrier whereupon the solutes therein will become dissolved in the water. To aid in this dispersion/solution process, a surfactant may be employed.

In the above description of pharmaceutical compositions containing a combination of active ingredients of the present invention, the equivalent expressions: "administration", "administration of", "administering", and "administering a" have been used with respect to the pharmaceutical compositions. As thus employed, these expressions are intended to mean providing to a patient in need of treatment a pharmaceutical composition of the present invention by the inhalation route of administration herein described, wherein the active ingredients are combinations of compounds of the present invention, or a prodrug, derivative, or metabolite thereof which is useful in treating an obstructive airways or other inflammatory disease, disorder, or condition in the patient. Accordingly, there is included within the scope of the present invention any other compound which, upon administration to a patient, is

capable of directly or indirectly providing a component compound of the present invention. Such compounds are recognized as prodrugs, and a number of established procedures are available for preparing such prodrug forms of the component compounds of the present invention.

The dosage and dose rate of the component compounds of the present invention effective for treating or preventing an obstructive airways or other inflammatory disease, disorder, or condition, will depend on a variety of factors, such as the nature of the component compound, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used, and the observations and conclusions of the treating physician.

For example, where the dosage form is topically administered to the bronchia and lungs, *e.g.*, by means of a powder inhaler, nebulizer, or other device known in the art, suitable dosage levels of the component compounds of the present invention will be between about 0.001 μg/kg and about 10.0 mg/kg of body weight per day, preferably between about 0.5 μg/kg and about 0.5 mg/kg of body weight per day, more preferably between about 1.0 μg/kg and about 0.1 mg/kg of body weight per day, and most preferably between about 2.0 μg/kg and about 0.05 mg/kg of body weight per day of the active ingredient.

Using representative body weights of 10 kg and 100 kg in order to illustrate the range of daily oral dosages which might be used as described above, suitable dosage levels of the component compounds of the present invention will be between about 1.0 and 10.0 μg and 500.0 and 5000.0 mg per day, preferably between about 50.0 to 500.0 μg and 50.0 and 500.0 mg per day, more preferably between about 100.0 and 1000.0 μg and 10.0 and 100.0 mg per day, and most preferably between about 200.0 and 2000.0 μg and about 5.0 and 50.0 mg per day of the active ingredient comprising a compound of Formula (1.0.0). These ranges of dosage amounts represent total dosage amounts of each active ingredient per day for a given patient. The number of times per day that a dose is administered will depend upon such pharmacological and pharmacokinetic factors as the half-life of each active ingredient, which reflects its rate of catabolism and clearance, as well as the minimal and optimal blood plasma or other body fluid

levels of each the active ingredient attained in the patient which are required for therapeutic efficacy.

Numerous other factors must also be considered in deciding upon the number of doses per day and the amount of each active ingredient per dose that will be administered. Not the least important of such other factors is the individual response of the patient being treated. Thus, for example, where the active ingredients are used to treat or prevent asthma, and are administered topically *via* aerosol inhalation into the lungs, from one to four doses consisting of actuations of a dispensing device, *i.e.*, "puffs" of an inhaler, will be administered each day, each dose containing from about 50.0 μg to about 10.0 mg of each the active ingredient.

A preferred delivery form of the pharmaceutical compositions of the present invention that is useful for inhalation administration of the combinations of compounds herein described is that of an aerosol spray presentation from a pressurised container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist) or nebulizer, with or without the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA), carbon dioxide, a further perfluorinated hydrocarbon such as perflubron or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomizer or nebulizer may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol (optionally, aqueous ethanol) or a suitable agent for dispersing, solubilizing or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. An aerosol is, in general terms, a colloid system in which the continuous phase, *i.e.*, the dispersion medium, is a gas. With reference to the pharmaceutical compositions herein described, an aerosol composition comprises a solution or suspension of a drug consisting of a combination of compounds of the present invention, which can be atomized into a fine mist for inhalation therapy. Thus, the aerosol composition comprises a liquid propellant and a particulate material.

In general, a suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1 μg to 10 mg of the active compounds of the formulation or a salt thereof and the actuation volume may vary from 1 to 100 μL. A typical formulation may comprise the active compounds of the formulation or salt thereof, propylene glycol, sterile water, ethanol, and sodium chloride.

Finely divided particles of drugs and suitable carriers therefor are widely used in the pharmaceutical industry and are especially important in the case of inhalation drugs where it is desired that the drug particles penetrate deep into the lung of a patient being treated. Effective use of an aerosol drug composition in the form of a suspension usually requires that the suspension comprise a uniform dispersion of the particulate matter in order to insure that an aerosol is produced that has the required components present in known amounts. A dispersion that is not homogeneous is usually the result of poor dispersibility of the particulate matter in the propellant and/or a tendency of the particulate matter to aggregate, sometimes to an extent that is irreversible.

The present invention is concerned with particulate-containing aerosol compositions consisting of inhaler suspensions used for the delivery of a particulate medicament comprising a combination of compounds of the present invention to the lungs or upper airway passages. The inhaler suspension is preferably held in a pressurized container fitted with a metering valve of fixed volume. Such a container is easy to use and portable, and assures that a known dose of the medicament is administered on each occasion of use. Containers of this type are referred to as metered dose inhalers.

It is essential that the inhaler suspension be consistently and homogeneously dispersed and that the performance of the metering valve be reproducible and effective throughout the life of the container. The inhaler suspension usually consists of the medicament particles dispersed in a liquefied gas which in use acts as a propellant. Once the valve stem of the metering valve is depressed, the propellant fraction of the metered dose rapidly vaporizes so as to aerosolize the suspended particulate medicament which is then inhaled by the user.

Heretofore, chlorofluorocarbons such as CFC-11, CFC-12 and CFC-14 have been employed as propellants in metered dose inhalers. It is important that a particulate medicament intended for pulmonary administration have a particle size with a median aerodynamic diameter between about 0.05 μm and about 11 μm. Larger particles will not necessarily or readily penetrate into the lungs and smaller sized particles are readily breathed out. On the other hand, particles between about 0.05 μm and about 11 μm can possess a high surface energy and therefore be difficult to disperse initially in the propellant, and once dispersed can exhibit a tendency to aggregate undesirably and rapidly, leading eventually to irreversible aggregation of the particles. Where CFC has been used as a propellant, this problem has been overcome by the addition of a surfactant soluble in the CFC, which coats the medicament particles and prevents their aggregation by means of steric hindrance. The presence of such a surfactant is also believed to be an aid to valve performance. Accordingly, in practice, medicament particles have been homogenized in liquid CFC-11 with the inclusion of a propellant soluble surfactant such as lecithin, oleic acid or sorbitan trioleate. The resulting bulk suspension has been dispensed into individual metered dose inhalers and a high vapor pressure propellant such as liquefied gas CFC-12/CFC-114 has then been added. These compositions have proven to be satisfactory in use, although the added surfactant can adversely affect the perceived taste of the inhaler in use. Oleic acid, *e.g.*, can impart a bitter taste.

Propellant CFC-11 (CCl_3F) and/or propellant CFC-114 ($CF_2Cl[CF_2Cl]$) with propellant CFC-12 (CCl_2F_2), however, are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants. The continued use of CFC propellants has therefore become unacceptable and has frequently been banned by local regulations. Alternative propellants which have been suggested for use in metered dose inhalers comprise fluorocarbons, hydrogen-containing fluorocarbons, notably HFA-134a and HFA-227, and hydrogen-containing chlorofluorocarbons, and a number of medicinal aerosol formulations using such propellant systems have been disclosed in the art.

Problems have been encountered in attempting to formulate the hydrofluoroalkanes into an aerosol composition such as an inhaler suspension. For example, the acceptable surfactants

which have been employed in CFC-based suspensions are not sufficiently soluble in hydrofluoroalkanes to prevent irreversible aggregation of the particulate medicament from occurring. Further, neither HFA-134a nor HFA-227 is a liquid at an acceptable temperature, so that bulk homogenization with particulate material prior to filling into individual pressurized containers is possible only if carried out under pressure. A number of proposals have, accordingly, been made in an attempt to employ hydrofluoroalkanes as the propellant in pressurized metered dose inhalers. For example, see WO 91/04011; WO 91/11495; WO 91/114422; WO 92/00107; WO 93/08446; WO 92/08477; WO 93/11743; WO 93/11744; and WO 93/11745. These published applications are all concerned with the preparation of pressurized aerosols for the administration of medicaments and seek to overcome the problems associated with the use of the new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared.

WO 92/06675 suggests the use of non-volatile co-solvents to modify the solvent characteristics of the hydrofluoroalkane propellant and thereby increase the solubility and hence permit the use of the surfactants traditionally employed in CFC-based metered dose inhalers. The co-solvent must be selected so that it does not result in less desirable aerosol properties or impart an unpleasant sharp taste to the formulation.

WO 91/11173 and WO 92/00061 suggest the use of alternative surfactants that are sufficiently soluble in HFA-134a and HFA-227, but such surfactants must be demonstrated to be free of any toxicity to humans.

WO 96/19968 suggests the use of a pharmaceutical formulation comprising a particulate medicament, at least one sugar, and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant. The particle size of the sugars employed in the formulations is the to be obtainable using conventional techniques such as milling and micronization, and the suspension stability of the aerosol formulations is the to be especially good.

WO 00/27363 discloses aqueous dispersions of nanoparticulate aerosol formulations, dry powder nanoparticulate aerosol formulations, propellant-based aerosol formulations, methods

of using the formulations in aerosol delivery devices, and methods of making such aerosol formulations. The nanoparticles in the aqueous dispersions or dry powder aerosol formulations comprise insoluble drug particles having a surface modifier thereon; and there is demonstrated the ability to aerosolize a concentrated nanoparticulate dispersion in an ultrasonic nebulizer which incorporates a fine mesh screen into its design. A therapeutic quantity of a concentrated nanoparticulate beclomethasone dipropionate formulation can be aerosolized in less than two seconds.

WO 00/00181 discloses compositions containing corticosteroid compounds present in a dissolved state, formulated in a concentrated, essentially non-aqueous form for storage, or in a diluted, aqueous-based form for ready delivery. The corticosteroid compositions contain ethoxylated derivatives of vitamin E and/or a polyethyleneglycol fatty acid ester as the high HLB surfactant present in the formulation. For example, beclomethasone dipropionate monohydrate is dissolved in a 2:1 wt./wt. mixture of PEG-200 and α-tocopherol polyethylene glycol succinate and then diluted with water, 1:6.65 by volume.

WO 99/47196 discloses methods and devices for delivering active agent formulations in dry powder or nebulized form, or in admixture with a propellant, the formulations being delivered at an inspiratory flow rate of <17 L/min, preferably 5-10 L/min. Bioavailability of the active agent is increased due to increased deposition of the active agent in the lung. A flow restrictor is used which comprises an aperture or set of apertures and a valving arrangement.

WO 99/16420 discloses stabilized dispersions that may be administered to the lung of a patient using a nebulizer, which comprise a stabilized colloidal system containing a perforated microstructure of the active agent dispersed in a fluorocarbon suspension medium. Density variations between the suspended particles and the suspension medium are minimized and the attractive forces between the microstructures are attenuated, so that the disclosed dispersions are particularly resistant to degradation, such as by settling or flocculation.

U.S. Patent No. 5,874,063 discloses finely divided particles of a pharmaceutical substance which, when exposed to water vapor, gives off heat of <1.2 J/g. Examples are given of

salbutamol sulfate (25%) and lactose (75%) conditioned with water at relative humidity 55-65%, of a non-conditioned micronized substance mixture (5-8 J/g), and of a conditioned micronized mixture (<0.5 J/g).

U.S. Patent No. 5,192,528 discloses pharmaceutical liposomes containing corticosteroids for the treatment of respiratory tract diseases. For example, a liposome suspension contains 95% egg phosphatidylcholine, 29.6 mg/mL; 95% egg phosphatidylglycerol, 0.9 mg/mL; beclomethasone dipropionate, 0.42 mg/mL; vitamin E, 0.172 mg/mL; Na_2HPO_4, 1.5 mg/mL; NaCl, 5.0 mg/mL; and water to 1.0 mL. The liposome suspension is aerosolized in a nebulizer at an air pressure of 10 psi to obtain aerosol particles with a mass median aerodynamic diameter of approximately 0.42 μm.

EP 338,670 discloses a solution of an inhalation drug packaged in a sealed disperser containing a pressurized gas and provided with a one-way outlet metering valve, that may be administered by nebulization. The dispenser may be prepared by introducing the solution and the pressurized gas into the dispenser under sterile conditions, or the dispenser may be sterilized after introduction of the solution and the pressurized gas. A preferred solution contains Na cromoglycate and chlorbutol for use in the treatment of obstructive airways diseases, and is prepared by dissolving chlorbutol in water at 20-60°C in a covered or sealed vessel, and admixing the resulting solution with solid Na cromoglycate.

U.S. Patent No. 4,908,382 discloses inhalation of a nebulized solution containing 10 mg furosemide and 7 mg NaCl with pH adjusted to 9 with a NaOH solution, which is effective in the treatment of asthmatic patients with exercise-induced bronchoconstriction.

GB 2,204,790 discloses mixtures of nedocromil Na with anti-cholinergic agents which are synergistic in the treatment of reversible obstructive airways diseases. An example of a nebulizer solution is one containing 0.5% (wt./vol.) nedocromil Na, 0.2% of atropine methonitrate, and water to 100%.

WO 87/00431 discloses treatment of bronchospastic disease characterized by airways hyper-reactivity by administration of gallopamil, a known Ca channel blocker. An example is a 3 mL nebulizer solution containing 1-20 mg gallopamil hydrochloride, 4% ethanol, and 4% propylene glycol in sterile saline, with pH adjusted to 6 with $NaHCO_3$.

EP 140,434 discloses pharmaceutical compositions with anticholinesterase, agonistic cholinergic, and antimuscarinic activity contained in a parasympathomimetic quaternary ammonium salt and a nasal carrier suitable for nasal administration. An example of a nebulizer solution is one containing neostigmine methylsulfate, 3 g; NaCl, 0.9 g; KH_2PO_4, 0.68 g; NaOH, 0.056 g; methyl *p*-hydroxybenzoate, 0.080 g; propyl *p*-hydroxybenzoate, 0.020 g; glycerin, 10 g; and water to 100 mL.

U.S. Patent No. 3,715,432 discloses aqueous aerosol compositions for inspiration into the alveoli in treatment of lung disorders, containing submicron (0.2-1 μ diameter) particles which are stable against evaporation; prepared by dispersing 100 mg to 5 g lecithin, *e.g.*, DL-dipalmitoyl-α-lecithin, in 100 mL water or isotonic saline solution; and nebulized by an ultrasonic generator at 25-75°C.

W0 95/01324 discloses a method and apparatus suitable for the formation of particulate drugs in a controlled manner utilizing a supercritical fluid particle formation system. The apparatus comprises a particle formation vessel with means for controlling the temperature and pressure of the vessel, together with means for the co-introduction into the vessel of a supercritical fluid and a vehicle containing at least one drug substance in solution or suspension, such that dispersion and extraction of the vehicle occur substantially simultaneously by the action of the supercritical fluid. The simultaneous co-introduction of the vehicle containing at least one drug substance in solution or suspension and the supercritical fluid, allows a high degree of control of parameters, *e.g.*, temperature, pressure and flow rate, of both vehicle fluid and supercritical fluid, at the exact point when they come into contact with one another. This gives a high degree of control over the conditions under which particles of the drug substance suspended or dissolved in the vehicle are formed, and thus of the resulting physical properties of the particles.

WO 95/31964 discloses a formulation suitable for nebulization comprising fluticasone propionate, substantially all of the particles of which have a particle size of <12 μm; one or more surfactants; one or more buffering agents; and water. An example of a nebulizer solution is one containing micronized fluticasone propionate, 0.525 mg; polyoxyethylene sorbitan monolaurate, 0.14 mg; sorbitan monolaurate, 0.018 mg; NaH_2PO_4, 18.80 mg; Na_2HPO_4, 3.50 mg; NaCl, 9.60 mg; and water to 2 mL.

WO 99/18971 discloses an aqueous nebulizer suspension containing water, mometasone furoate monohydrate, a nonionic surfactant, a soluble salt, and optionally a pH buffer. The suspension is prepared by ultra-sonication or jet milling techniques. An example of a nebulizer solution is one containing mometasone furoate, 500 mg; Polysorbate-80, 50 mg; citric acid monohydrate, 181 mg; sodium citrate dihydrate, 335 μg; sodium chloride, 9 mg; and water q.s. 1 mL. The suspension has a median particle size of 1.24 μm and a mean particle size of 1.34 μm.

WO 96/25919 discloses an aerosol comprising droplets of an aqueous dispersion of nanoparticles comprising beclomethasone particles having a surface modifier on the surface thereof. An example of a nebulizer solution is one containing a suspension of 2.5% beclomethasone dipropionate in an aqueous solution of polyvinyl alcohol as a surface modifier. The nanoparticles have a particle size distribution of 0.26 μm.

WO 96/22764 discloses pharmaceutical liposomes or dehydrated liposomes for use in the treatment of asthma by inhalation therapy. An example of a nebulizer solution is one containing 9α-chloro-6α-fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carboxylate and one or more synthetic phospholipids, especially 1-*N*-hexadecanoyl-2-(9-*cis*-octadecenoyl)-3-sn-phosphatidylcholine, 700 mg; and Na 1,2-di(9-*cis*-octadecenoyl)-3-sn-phosthatidylserine, 300 mg dissolved in *tert*-BuOH, and the solution thereby obtained mixed with 100 mg of the above-recited 17β-carboxylate dissolved in 5 mL *tert*-BuOH. The resulting solution is added dropwise to 200 mL phosphate-buffered saline

solution, and the aqueous liposome suspension is dialyzed against PBS and concentrated to 20 mL, filtered, and dispensed into vials for administration by nebulizer.

As already indicated, finely divided drug particles are prepared by conventional methods that involve micronization or grinding, although a number of other techniques are also available for their production. Micronization can produce particles which have regions of partially amorphous structure, but which are generally sufficiently stable for pharmaceutical use. However, these particles are liable to change their structure when kept in an adverse environment, such as during storage of a drug when conditions of high humidity that cause agglomeration may be encountered. Such adverse conditions can also be encountered during use of the drug by a patient. Drug particles produced by conventional methods often give off significant amounts of heat when exposed to water vapor. It is known in the art that this problem can be avoided by surface treatment of the particles without substantially altering their particle size. An added benefit of such treated particles is that they help to increase the respirable fraction of drugs in powder form when used in dry powder inhalation devices. Such particles have also been found to have a greater degree of crystallinity than more conventional fine particles. Preferably such particles give off less than 1.0 J/g, more preferably less than 0.5 J/g, and most preferably less than 0.1 J/g.

The particle size of drug substances in finely divided form, where it is desired that such particles enter deep into the lung of a patient being treated, should be <10 μm, and is preferably in the range of 0.1 to 10 μm. Where excipients in finely divided form are used as carriers for such particulate drug substances, they may be of a particle size of <10 μm, and preferably are in the range of 0.1 to 10 μm. In those cases when it is desired that the excipient does not enter the lung to any appreciable extent, the excipient particles may have a size of up to about 120 μm, *e.g.*, of from about 30 to about 120 μm. The size of a particle of either a drug substance or an excipient may be measured using a Malvern Master Sizer, a Coulter Counter, or a microscope. Such particles sizes are usually expressed as mass median diameters.

The total surface area of the particulate drug substances and their excipients which comprise the pharmaceutical compositions of the present invention is also an important criterion.

Surface areas of the particles are determined by BET gas absorption, *e.g.*, as measured by a Flowsorb II 2300 or Gemini 2370, available from Micromeritics Co., USA, and should be from 3 to 12 m^2/g, and preferably of from 3 to 9 m^2/g.

The weight ratio of particulate drug substances to their excipients which are utilized in the pharmaceutical compositions of the present invention is preferably in the range of 1:1 to 1:1000, respectively, and more preferably in the range of 1:1 to 1:500, and most preferably in the range of 1:1 to 1:200.

Suitable excipients for use in the pharmaceutical compositions of the present invention are selected from those which are generally recognized as safe for inhalation use, and include, *e.g.*, carbohydrates, including sugars, *e.g.*, lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, xylitol, mannitol, myoinositol, raffinose, maltitol, and melezitose. Other suitable excipients include amino acids, *e.g.*, alanine and betaine; and compounds which enhance the absorption of drug substances in the lung, such as surfactants, *e.g.*, alkali metal salts of fatty acids, including sodium tauro-dihydrofusidate, lecithins, sodium glycocholate, sodium taurocholate, and octylglucopyranoside. Other types of excipients useful in forming the pharmaceutical compositions of the present invention include anti-oxidants, *e.g.*, ascorbic acid; and buffer salts.

All of the substances which are components of the pharmaceutical compositions of the present invention can be used in the form of solvates, *e.g.*, hydrates; esters; or salts; or in the form of solvates or hydrates of such salts or esters.

In certain embodiments of the present invention, the method disclosed in above-mentioned W0 95/01324 is used, including an apparatus suitable for the formation of particulate drugs in a controlled manner utilizing a supercritical fluid particle formation system. An aerosol pharmaceutical formulation prepared in accordance with this method comprises a combination of compounds of the present invention having a controlled particle size, shape and morphology, together with a fluorocarbon, hydrogen-containing fluorocarbon or hydrogen-containing chlorofluorocarbon propellant. In particular, use of particulate crystalline

forms of the component compounds can provide benefits consisting of a reduction in the rates of agglomeration and deposition of drug substance onto aerosol can walls, actuator and valve components. Use of such particulate crystalline forms may also permit the formation of stable dispersions using little or no additional components such as surfactants or co-solvents. It is also possible to reduce the adsorption of drug substances into the rubber components of the valve and/or actuator parts of the delivery device. A further benefit of minimizing or eliminating the use of formulation excipients such as surfactants and co-solvents is a formulation that may be substantially taste and odor free, less irritating and less toxic than conventional formulations. Preferably the propellant is 1,1,1,2-tetrafluoroethane (HFA 134a), in which formulations the weight ratio of drug to propellant is preferably between 0.025:75 and 0.1:75, for example, 0.05:75.

Preparation of particles using the supercritical fluid particle formation method also permits control over the quality of the crystalline and polymorphic phases of those particles. Many of the compound components of the combinations of the present invention exist in two or more polymorphic forms, and it is desirable to provide the best particulate forms for these polymorphs as well. It is possible to achieve such quality control because the particles will experience the same stable conditions of temperature and pressure when formed. This method also affords the potential for enhanced purity of the particulate final product, which is a result of the high selectivity of supercritical fluids under different working conditions, that in turn enables the extraction of one or more impurities that may be present from the vehicle containing the drug substance of interest.

Co-introduction of the vehicle and supercritical fluid, leading to simultaneous dispersion and particle formation, allows particle formation to be carried out at temperatures at or above the boiling point of the vehicle, enabling operation of the process in temperature and pressure domains which allow the formation of particulate products not otherwise achievable. Thus, control of parameters such as size and shape in the particulate product will depend upon the operating conditions used when carrying out the supercritical fluid method. Variables include the flow rates of the supercritical fluid and/or of the vehicle containing the drug substance, the

concentration of the drug substance in the vehicle, and the temperature and pressure inside the particle formation vessel.

Aerosol pharmaceutical formulations containing compound combinations of the present invention are prepared in a form having a dynamic bulk density of $<0.1 g/cm^{-3}$, preferably in a range of between 0.01 and 0.1 g/cm^{-3} and, more preferably, in the range of between 0.01 and 0.075 g/cm^{-3}, together with a fluorocarbon, hydrogen-containing fluorocarbon or hydrogen-containing chlorofluorocarbon propellant. The dynamic bulk density (W) is indicative of a substance's fluidizability and is defined as:

$$W = \frac{(P - A)C}{100} + A$$

where P is the packed bulk density (g/cm^{-3}), A is the aerated bulk density (g/cm^{-3}), and C is the compressibility (%) where C is calculated by the equation:

$$C = \frac{P - A}{P} \times 100$$

In those cases where the value of W is low, there is a correspondingly high degree of fluidizability.

When crystallized compound components of the present invention prepared by other conventional methods are compared to those prepared by the above-described supercritical fluid particle formation method, both before and after micronization, the component compounds exhibit a significantly lower dynamic bulk density. It will be appreciated that in the case of an inhaled pharmaceutical, it is particularly desirable to produce a drug substance which is readily fluidizable, thereby potentially improving its inhalation properties. Thus, the component compounds used in the formulations of the present invention are observed to have improved handling and fluidizing characteristics compared with the compounds crystallized by other conventional methods.

Preferably, the of the present invention are within a particle size range suitable for pharmaceutical dosage forms to be delivered by inhalation or insufflation. A suitable particle size range for this use is 1 to 10 μm, preferably 1 to 5 μm. The particles also generally have a

uniform particle size distribution, as measured by a uniformity coefficient of from 1 to 100, typically 1 to 20, *e.g.*, 5 to 20.

The drug substances employed in the pharmaceutical formulations of the present invention typically have a low cohesivity, for example of 0 to 20%, preferably 0 to 5%, as established by methods of measurement based on those described by R.L. Carr in *Chemical Engineering*, 163-168, 1965.

Conventionally crystallized component compounds used in the present invention may also be studied by differential scanning calorimetry (DSC) in order to show any transition between two or more polymorphic forms that may exist. Use of the above-described supercritical fluid particle formation method allows the preparation of substantially pure polymorphs or controlled mixtures of the polymorphic forms. The thus prepared polymorphs are also stable, meaning that there is no transition from one polymorph to another observed under DSC conditions. By "substantially pure" polymorph is meant a composition containing a first polymorph, but essentially none of the other polymorph(s); and by "essentially none" is meant less than 0.5% w/w based upon the first polymorph, *e.g.*, 0.1% or less.

A component compound of the present invention prepared by the above-described supercritical fluid particle formation method may be used to prepare a pharmaceutical composition which further comprises a pharmaceutically acceptable carrier. Preferred carriers for this purpose include polymers, *e.g.*, starch and hydroxypropylcellulose; silicon dioxide; sorbitol; mannitol; and lactose, *e.g.*, lactose monohydrate. Using the above-described supercritical fluid particle formation method, a component compound and a carrier may be co-crystallized together to form multi-component particles comprising both the component compound and the carrier. Pharmaceutical formulations of the present invention comprise the multi-component particles together with a fluorocarbon, hydrogen-containing fluorocarbon, or hydrogen-containing chlorofluorocarbon propellant. Preferred embodiments of the present invention include a pharmaceutical composition comprising a component compound together with lactose in the form of multi-component particles.

For further details concerning the use of supercritical fluids, see J.W. Tom and P.G. Debendetti, "Particle Formation with Supercritical Fluids - A Review", *J. Aerosol. Sci.*, 22 (5), 555-584 (1991). A supercritical fluid can be defined as a fluid existing simultaneously at or above its critical pressure (P_C) and its critical temperature (T_C). Supercritical fluids are characterized by high diffusivity, low viscosity, and low surface tension compared with other non-supercritical liquids. The significant compressibility of supercritical fluids compared with that of the ideal gas implies large changes in fluid density in response to slight changes in pressure, which in turn means highly controllable solvation power. Supercritical fluid densities typically range from 0.1-0.9 g/mL under normal working conditions. Consequently, selective extraction with one supercritical fluid is possible.

Many supercritical fluids are normally gases under ambient conditions, thereby eliminating the evaporation/concentration step needed with conventional liquid extraction. Further, most of the commonly used supercritical fluids create non-oxidizing or non-degrading atmospheres due to their inertness and the moderate temperatures which may be employed during routine working, thus providing a protective environment for sensitive and thermolabile compounds. Carbon dioxide is the most extensively used supercritical fluid due to its cheapness, non-toxicity, non-flammability and low critical temperature.

As a result of the above-described characteristics of supercritical fluids, several techniques of extraction and particle formation have been developed which utilize supercritical fluids, in addition to that described in the above-mentioned W0 95/01324.

As used herein, the term "supercritical fluid" means a fluid at or above its critical pressure (P_C) and critical temperature (T_C) simultaneously. In practice, the pressure of the fluid is likely to be in the range of from 1.01 P_C - 7.0 P_C, and its temperature in the range of from 1.01 T_C, - 4.0 T_C. The term "vehicle" as used herein means a fluid which dissolves a solid or solids, to form a solution, or which forms a suspension of a solid or solids which do not dissolve, or else have a low solubility in the fluid. The vehicle can be composed of one or more fluids.

As used herein, the term "supercritical solution" means a supercritical fluid which has extracted and dissolved the vehicle. The term "dispersion" as used herein means the formation of droplets of the vehicle containing at least one drug substance in solution or suspension. The term "particulate product" as used herein includes products in a single-component or multi-component form, *e.g.*, as an intimate mixture of one component in a matrix of another component.

Supercritical fluids for use as described herein include carbon dioxide, nitrous oxide, sulphur hexafluoride, xenon, ethylene, chlorotrifluoromethane, ethane, and trifluoromethane. Carbon dioxide is an especially preferred choice as supercritical fluid. The supercritical fluid may optionally contain one or more modifiers, *e.g.*, methanol, ethanol, isopropanol or acetone. When used, the modifier preferably constitutes not more than 20%, and more particularly constitutes between 1 and 10%, of the supercritical fluid. The term "modifier" as used herein is well known to those persons skilled in the art. Accordingly, a modifier (or co-solvent) may be described as a substance which, when added to a supercritical fluid, changes the intrinsic properties of the supercritical fluid at or about the critical point. It will be appreciated that the precise conditions of operation of the process described herein will be dependent upon the choice of supercritical fluid and whether or not any modifiers are present.

It is preferred to maintain the pressure inside the particle formation vessel substantially in excess of the Pc, *e.g.*, 100-300 bar for carbon dioxide, while the temperature is maintained slightly above the Tc, *e.g.*, 40-600°C for carbon dioxide. The flow rates of the supercritical fluid and/or the vehicle may also be controlled so as to achieve a desired particle size, shape and/or form. Typically, the ratio of the vehicle flow rate to the supercritical fluid flow rate is between 0.001 and 0.1, preferably between 0.01 and 0.07, and more preferably around 0.03. The method preferably additionally involves collecting the particulate product following its formation, and may also involve recovering the supercritical solution formed, separating the components of the solution, and recycling one or more of those components for future use. It will be appreciated that the choice of a suitable combination of supercritical fluid, modifier, if any, and vehicle is well within the capabilities of a person of ordinary skill in the art.

Use of an automated back-pressure regulator such as model number 880-81 produced by Jasco Inc. can eliminate pressure fluctuation across the particle formation vessel and ensure a more uniform dispersion by the supercritical fluid of the vehicle containing the drug substance, with narrow droplet size distribution, during the particle formation process. The dispersed droplets are unlikely to reunite to form larger droplets, since the dispersion occurs by the action of the supercritical fluid, which also ensures thorough mixing with the vehicle and rapidly removes the vehicle from the drug substance, leading to particle formation. The means for co-introduction of the supercritical fluid and the vehicle into the particle formation vessel should allow for concurrent directions of flow, preferably by means of a coaxial nozzle. This procedure ensures no contact between the formed particles and the vehicle fluid around the nozzle tip area. Such contact reduces control of the final product size and shape.

Further control over droplet size in addition to that provided by the above-described nozzle design, is achieved by managing the flow rates of the supercritical fluid and the vehicle fluid. Also, retaining the particles in the particle formation vessel eliminates the potential of contact with the vehicle fluid that might otherwise take place on depressurizing of the supercritical solution. Such contact would alter the shape and size, and potentially the yield, of the particulate product. Another advantage of the above-described method is that it can allow particle formation to occur in a completely closed environment in which the apparatus is sealed from the atmosphere. This facilitates the maintenance of sterile operating conditions and the elimination of oxygen, moisture, or other contaminants. It also reduces the risk of environmental pollution.

The final aerosol pharmaceutical formulation of the present invention desirably contains 0.03-0.13% w/w, preferably 0.07% w/w, of medicament relative to the total weight of the formulation.

Suitable propellants for use in the pharmaceutical compositions of the present invention comprise any fluorocarbon, hydrogen-containing fluorocarbon, or hydrogen-containing chlorofluorocarbon or mixtures thereof having a sufficient vapor pressure to render them effective as propellants. Preferably, the propellant will be a non-solvent for the medicament

involved. Suitable propellants include (C_1-C_4) hydrogen-containing chlorofluorocarbons, *e.g.*, CH_2ClF, $CClF_2CHClF$, CF_3CHClF, CHF_2CClF_2, $CHClFCHF_2$, CF_3CH_2Cl, and $CClF_2CH_3$; (C_1-C_4) hydrogen-containing fluorocarbons, *e.g.*, CHF_2CHF_2, CF_3CH_2F, CHF_2CH_3, and CF_3CHFCF_3; and perfluorocarbons, *e.g.*, CF_3CF_3 and $CF_3CF_2CF_3$.

Where mixtures of fluorocarbon, hydrogen-containing fluorocarbon, or hydrogen-containing chlorofluorocarbon propellants are employed, they may be mixtures of the above-identified propellant compounds, or they may be mixtures, preferably binary mixtures, with other fluorocarbon, hydrogen-containing fluorocarbon, or hydrogen-containing chlorofluorocarbon propellants, *e.g.*, $CHClF_2$, CH_2F_2, and CF_3CH_3. Preferably, a single fluorocarbon, hydrogen-containing fluorocarbon, or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are (C_1-C_4) hydrogen-containing fluorocarbons, *e.g.*, 1,1,1,2-tetrafluoroethane, CF_3CH_2F; and 1,1,1,2,3,3,3-heptafluoro-*n*-propane, CF_3CHFCF_3, especially 1,1,1,2-tetrafluoroethane. It is preferred, but not required, that propellants are used which do not degrade stratospheric ozone. Accordingly, it is preferred that the pharmaceutical formulations of the present invention be substantially free of chlorofluorocarbons, *e.g.*, CCl_3F, CCl_2F_2, and CF_3CCl_3.

The propellant used in preparing the pharmaceutical compositions of the present invention may additionally contain a volatile adjuvant such as a saturated hydrocarbon, *e.g.*, propane, *n*-butane, isobutane, pentane, and isopentane; or a dialkyl ether, *e.g.*, dimethyl ether. Up to 50% w/w of the propellant which is being used may comprise a volatile hydrocarbon, *e.g.*, 1-30% w/w. Preferably, however, pharmaceutical formulations of the present invention are substantially free of volatile adjuvant.

It is not required that the pharmaceutical compositions of the present invention contain a surfactant or a co-solvent, and it is not necessary to pre-treat the medicament prior to dispersal in the propellant. However, certain pharmaceutical formulations of the present invention may include liquid components of higher polarity than the propellant employed. Such polarity may be determined by the method described in EP 327,777. Where such components of higher polarity are included, alcohols, *e.g.*, ethanol, are preferable. Such higher polarity liquid

components are preferably included at relatively low concentrations, *e.g.*, <5%, preferably <1% w/w, based on the total weight of fluorocarbon or hydrogen-containing chlorofluorocarbon present. Preferred pharmaceutical formulations of the present invention contain essentially no higher polarity liquid components, *i.e.*, <0.1% w/w, based on total weight of propellant, *e.g.*, 0.0001% or less.

Where a surfactant is employed in the pharmaceutical compositions of the present invention, it is selected from those which are physiologically acceptable upon administration by inhalation, *e.g.*, oleic acid; sorbitan trioleate (Span® 85); sorbitan mono-oleate; sorbitan monolaurate; polyoxyethylene (20) sorbitan monolaurate; polyoxyethylene (20) sorbitan monooleate; natural lecithin; fluorinated and perfluorinated surfactants including fluorinated lecithins; fluorinated phosphatidylcholines; oleyl polyoxyethylene (2) ether; stearyl polyoxyethylene (2) ether; lauryl polyoxyethylene (4) ether; block copolymers of oxyethylene and oxypropylene; synthetic lecithin; diethylene glycol dioleate; tetrahydrofurfuryl oleate; ethyl oleate; isopropyl myristate; glyceryl monooleate; glyceryl monostearate; glyceryl mono-ricinoleate; cetyl alcohol; stearyl alcohol; polyethylene glycol 400; cetyl pyridinium chloride; benzalkonium chloride; olive oil; glyceryl monolaurate; corn oil; cotton seed oil; and sunflower seed oil.

Embodiments of the present invention comprising a pharmaceutical formulation in which the particulate medicament is pre-coated with surfactant, preferably contain substantially a non-ionic surfactant having reasonable solubility in substantially non-polar solvents, since it facilitates coating of the medicament particles when using solvents in which the medicament has limited or minimal solubility. The particulate drug substance with its dry coating of surfactant may then be suspended in propellant, optionally with a co-solvent such as ethanol. These types of pharmaceutical formulations are well known in the art and are described in WO 92/08446 and WO 92/08447.

The pharmaceutical compositions of the present invention may be prepared by dispersal of the combination of particulate drug substances and the pharmaceutically acceptable carrier in the selected propellant in an appropriate container with the aid, *e.g.*, of sonication. This preparation process is preferably carried out under anhydrous conditions in order to prevent

any adverse effects on suspension stability from moisture. Chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations of the present invention may be determined using techniques that are well known in the art. For example, chemical stability of the components may be determined by HPLC assay of the overall formulation after storage for a prolonged period of time. Physical stability data may be obtained from analytical techniques, *e.g.*, leak testing, valve delivery assay based on average shot weights per actuation, dose reproducibility assay based on active ingredient per actuation, and spray distribution analysis.

The particle size distribution of the aerosol formulations of the present invention may be measured by conventional techniques, *e.g.*, by cascade impaction, or by twin impinger analysis as described in *British Pharmacopoeia*, A204-207, Appendix XVII C, 1988. Using this technique, the "respirable fraction" may be calculated, which, as used herein, means the amount of active ingredient collected in the lower impingement chamber per actuation, expressed as a percentage of the total amount of active ingredient delivered per actuation. The pharmaceutical formulations of the present invention containing the combination of compounds as described herein of mean particle size between 1 and 10 μm, preferably have a respirable fraction of 30% or more by weight of the medicaments, more preferably 30-70% by weight, *e.g.*, 30-50% by weight, based on the total weight of the medicaments.

The pharmaceutical formulations of the present invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Such canisters generally comprise a container capable of withstanding the vapor pressure of the propellant employed, *e.g.*, a plastic or plastic-coated glass bottle, or preferably a metal can, *e.g.*, an aluminum can that is optionally anodized, lacquer-coated, and/or plastic-coated, the container being closed with a metering valve. Canisters lined with a fluorocarbon polymer, especially polytetrafluoroethylene, PTFE, in combination with a non-fluorocarbon polymer, especially polyethersulfone, PES, are preferred. Typical metering valves are designed to deliver a metered amount of the pharmaceutical formulation per actuation, and usually incorporate a gasket to prevent leakage of propellant through or around the valve. The gasket may comprise any suitable elastomeric material, *e.g.*, low density polyethylene; chlorobutyl rubber; black and white butadiene-

acrylonitrile rubbers; butyl rubber; and neoprene. Suitable valves are available from a number of different manufacturers.

Conventional bulk manufacturing methods and machinery well known in the art may be employed in the preparation of large scale batches for the commercial production of filled canisters. For example, in one bulk manufacturing method, a metering valve is crimped onto an aluminum can to form an empty canister. The particulate medicament is thereafter added to a charge vessel and liquefied propellant is pressure filled through the charge vessel into a manufacturing vessel. The particulate medicament suspension is mixed before recirculation to a filling machine, and an aliquot of the medicament suspension is then filled through the metering valve into the canister. Each filled canister is check-weighed, coded with a batch number, and packed into a tray for storage prior to release testing.

Each filled canister is conveniently fitted into a suitable channeling device to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Channeling devices comprise, *e.g.*, a valve actuator and a cylindrical or cone-like passage through which the medicament may be delivered from the filled canister *via* the metering valve to the nose or mouth of a patient. Metered dose inhalers are typically designed to deliver a fixed unit dosage of medicament per actuation, *e.g.*, in the range of 10-500 μg of medicament per puff. However, the actual amount of medicament administered per day to a patient will depend upon the age and condition of that patient, the particular medicaments being administered, and the frequency of administration of the medicaments. When combinations of medicaments are employed as in the case of the present invention, the dose of each component of the combination will generally be that employed for each component when used alone. Typically, administration may be one or more times, *e.g.*, 1-8 times per day, with 1-4 puffs being inhaled during each individual administration. Each filled canister for use in a metered dose inhaler contains anywhere from about 60 to about 240 doses or puffs of medicament.

Preparations and Working Examples

There follows a description of numerous Examples showing preparation of pharmaceutical compositions containing a combination of therapeutic agents in accordance with the present invention. These Examples are intended to further illustrate the combinations of therapeutic agents of the present invention, pharmaceutical compositions containing them, and processes in accordance with which the pharmaceutical compositions may be readily prepared by the artisan. The artisan will be aware of many other suitable processes and pharmaceutically acceptable carriers that are also available, as well as acceptable variations in the procedures and ingredients described below.

The description which follows is for the purpose of illustrating the present invention and is not intended to in any way create limitations, express or implied, upon the scope of the present invention. The claims appended hereto are for the purpose of reciting the present invention, of expressing the contemplated scope thereof, and of pointing out particulars thereof.

Example 1

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

9-[(2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

tiotropium bromide

trichloromonofluoromethane

dichlorotetrafluoroethane

dichlorodifluoromethane

soya lecithin

Example 2

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-2-yl]methyl}-2-phenylacetamide

tiotropium bromide

dichlorotetrafluoroethane

trichloromonofluoromethane

dichlorodifluoromethane

soya lecithin

Example 3

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-2-yl]methyl}benzamide

tiotropium bromide

dichlorotetrafluoroethane

trichloromonofluoromethane

dichlorodifluoromethane

soya lecithin

Example 4

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)-amino]-9*H*-purin-2-yl]methyl}benzenesulfonamide

tiotropium bromide

trichloromonofluoromethane

dichlorotetrafluoroethane

dichlorodifluoromethane

soya lecithin

Example 5

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

(2*R*,3*R*,4*S*,5*R*)-2-[2-(benzylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol

dichlorotetrafluoroethane

tiotropium bromide

ethanol

dichlorodifluoromethane

ascorbic acid

Example 6

A package in the form of a non-pressurized glass vial is prepared which may be used for administration of the active ingredients as an aerosol mist by hand-bulb nebulizer, compressed

air or oxygen operated nebulizer, or by an intermittent positive pressure breathing (IPPB) device.

The contents of each the vial are as follows:

(2*R*,3*R*,4*S*,5*R*)-2-[2-(cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol
sodium metabisulfite
tiotropium bromide
glycerin or saccharin sodium
chlorobutanol
citric acid or sodium citrate
purified water
sodium chloride

Example 7

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

(2*R*,3*R*,4*S*,5*R*)-2-[2-{[(cyclohexylmethyl)amino]-methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol
tiotropium bromide
sorbitan trioleate
trichloromonofluoromethane
dichlorodifluoromethane

Example 8

A package in the form of a pressurized, tetrafluoroethylene-coated aluminum canister for use in a metered dose inhaler is prepared which is sufficient to provide about 200 actuations of the inhaler, each actuation providing about 20 μg of each active ingredient.

The contents of each the canister are as follows:

(2*R*,3*R*,4*S*,5*R*)-2-[2-[(cyclopentylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol

tiotropium bromide

oleic acid

trichloromonofluoromethane

dichlorodifluoromethane

Example 9

A package in the form of a non-pressurized glass vial is prepared which may be used for administration of the active ingredients as an aerosol mist by hand-bulb nebulizer, compressed air or oxygen operated nebulizer, or by an intermittent positive pressure breathing (IPPB) device.

The contents of each the vial are as follows:

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-1-propanesulfonamide

tiotropium bromide

sodium chloride

sulfuric acid

benzalkonium chloride

purified water

Example 10

A package in the form of a double-foil blister strip in which each blister contains a powder formulation is prepared. The package is designed for use with a device that opens each the blister when the device is actuated. The active ingredients are dispersed from the blister into the air stream created when the patient inhales through the mouthpiece of the device.

The dry powder contents of each the blister are as follows:

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol

lactose

tiotropium bromide

We Claim:

1. A pharmaceutical composition comprising:

(i) an adenosine A_{2A} receptor agonist agent; and

(ii) an anti-cholinergic agent,

wherein the combination is therapeutically effective in the treatment of an obstructive airways disease when administered by inhalation.

2. A pharmaceutical composition comprising:

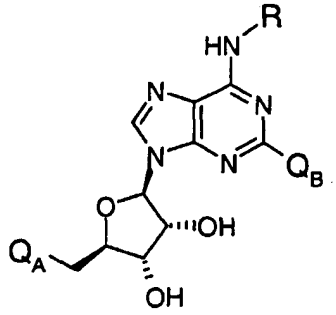
(i) an adenosine A_{2A} receptor agonist agent; and

(ii) an anti-cholinergic agent comprising tiotropium and derivatives thereof,

wherein the combination is therapeutically effective in the treatment of an obstructive airways disease when administered by inhalation.

3. The pharmaceutical composition according to one of claims 1 or 2, wherein the obstructive airways disease is asthma, COPD, or other obstructive airways disease exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm.

4. The pharmaceutical composition according to one of claims 1 or 2, wherein the adenosine A_{2A} receptor agonist agent comprises a compound of Formula (3.0.1):



(3.0.1)

wherein:

Q_A is $-OR^1$, $-C(=O)NHR^3$, $-R^5$, or $-R^7$, wherein

R^1 is -H, (C_1-C_4) alkyl, or cyclopropylmethyl;

R^3 is -H, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, cyclopropylmethyl, phenyl, naphthyl, azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, or HET, where the azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl are substituted by 0 or 1 of (C_1-C_6) alkyl, wherein

HET is C-linked pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoxazolyl, or quinoxalinyl, each substituted by 0-3 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or halo;

R^5 is $-CH_2OH$ or $-C(=O)NR^{14}R^{16}$, wherein

R^{14} and R^{16} are each independently -H, or (C_1-C_6) alkyl substituted by 0 or 1 of cyclopropyl;

R^7 is a C-linked, 5-membered aromatic heterocycle containing (a) 1-4 ring nitrogen atoms, or (b) 1-2 ring nitrogen atoms and 1 oxygen or 1 sulfur ring atom, where the heterocycle is substituted by 0 or 1 (C_1-C_6) alkyl substituted by 0 or 1 of phenyl, -OH, (C_1-C_6) alkoxy, or $-NR^{18}R^{20}$, wherein

R^{18} and R^{20} are each independently -H, (C_1-C_6) alkyl, or taken together with the nitrogen atom to which they are attached, are azetidinyl, pyrrolidinyl, or piperidinyl, each substituted by 0 or 1 of (C_1-C_6) alkyl; and

Q_B is $-(CH_2)_n$-A-R^9, $-C(=O)N(R^{11})$-B-R^{13}, $-CH_2$-$NHS(=O)_2$-B-R^{15}, or -L-D-$N(R^{17})$-E-$NR^{19}R^{21}$, wherein

n is 1 or 2, and

A is $-NR^{22}$-, $-NR^{22}C(=O)$-, $-NR^{22}C(=O)NR^{24}$-, $-NR^{22}C(=O)O$-, $-OC(=O)NR^{22}$-, $-C(=O)NR^{22}$-, $-NR^{22}S(=O)_2$-, $-S(=O)_2NR^{22}$-, -O-, -S-, or $-S(=O)_2$-, wherein

R^{22} and R^{24} are each independently -H, (C_1-C_4) alkyl, or benzyl substituted by 0-3 of (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo, or cyano;

R^9 is a group of the formula $-(CH_2)_p$-R^{26}-W, wherein

p is 0, 1, or 2,

R^{26} is a bond, (C_1-C_4) alkylene, (C_3-C_7) cycloalkylene, phenylene, or naphthylene, the cycloalkylene, phenylene, and naphthylene each substituted by 0-3 of (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo, or (C_1-C_4) alkoxy(C_1-C_4) alkylene, and

W is a member selected from the group consisting of:

(a) -H, $-NR^{28}R^{30}$, $R^{28}R^{30}N$-alkylene-, $-OR^{28}$, $-C(=O)OR^{28}$, $-OC(=O)R^{28}$, $-S(=O)_2R^{28}$, -CN, $-S(=O)_2NR^{28}R^{30}$, $-NR^{28}C(=O)R^{30}$, $-NR^{28}S(=O)_2R^{30}$, or $-C(=O)NR^{28}R^{30}$; wherein R^{28} and R^{30} are the same or different and are selected from the group consisting of -H, (C_1-C_4) alkyl, phenyl and benzyl,

provided that:

(i) when W is $-OC(=O)R^{28}$, $-S(=O)_2R^{28}$, $-NR^{28}C(=O)R^{30}$, or $-NR^{28}S(=O)_2R^{30}$, then the terminal R^{30} is not -H; and

(ii) R^{26} is a bond, p is 0, and W is -H only when A is $-NR^{22}$, $-NR^{22}C(=O)NR^{24}$, $-OC(=O)NR^{22}$, $-C(=O)NR^{22}$, $-S(=O)_2NR^{22}$, -O-, or -S-;

(b) an optionally-substituted, fully- or partially-saturated or -unsaturated, mono- or bicyclic, heterocyclic group, which is linked to R^{26} by a ring carbon atom; and

(c) N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, each substituted by 0-3 (C_1-C_4) alkyl; with the proviso that $-(CH_2)_p-R^{26-}$ is not $-CH_2-$; and

where A is $-NR^{22}-$, $-C(=O)NR^{22}-$, $-OC(=O)NR^{22}-$, or $-S(=O)_2NR^{22}-$, R^{22} and R^9 may be taken together with the nitrogen atom to which they are attached to form an azetidine, pyrrolidine, piperidine, or piperazine ring, substituted by 0-3 of (C_1-C_4) alkyl;

R^{11} is -H or (C_1-C_6) alkyl;

B is a bond or (C_1-C_6) alkylene; and

R^{13} is a member selected from the group consisting of:

(a) -H; (C_1-C_6) alkyl; $-C(=O)OR^{32}$; -CN; $-C(=O)NR^{32}R^{34}$; -(C_3-C_8) cycloalkyl; phenyl; or naphthyl, where the -(C_3-C_8) cycloalkyl, phenyl, or naphthyl is substituted by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy(C_1-C_6)alkyl, $R^{32}R^{34}N(C_1$-$C_6)$alkyl, halo(C_1-C_6)alkyl, fluoro(C_1-C_6)alkoxy, (C_2-C_5) alkanoyl, halo, $-OR^{32}$, cyano, $-C(=O)OR^{32}$, (C_3-C_8) cycloalkyl, $-S(=O)_mR^{35}$ where m is 0, 1, or 2, $-NR^{32}R^{34}$, $-S(=O)_2NR^{32}R^{34}$, $-C(=O)NR^{32}R^{34}$, $-NR^{32}C(=O)R^{35}$, or $-NR^{32}S(=O)_2R^{35}$; with the proviso that R^{13} is not -H when B is a bond;

(b) $-NR^{32}R^{34}$; $-OR^{32}$; $-C(=O)OR^{32}$; $-OC(=O)R^{34}$; $-S(=O)_2R^{34}$; -CN; $-S(=O)_2NR^{32}R^{34}$; $-NR^{32}COR^{34}$; or $-C(=O)NR^{32}R^{34}$; when B is (C_2-C_6) alkylene;

(c) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle having either from 1 to 4 ring nitrogen atom(s), or 1 or 2 nitrogen and 1 oxygen or 1 sulfur ring atoms;

C-substituted by 0-2 of oxo, $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkoxy, $R^{36}R^{38}N(C_1\text{-}C_6)$ alkyl, halo$(C_1\text{-}C_6)$ alkyl, fluoro$(C_1\text{-}C_6)$ alkoxy, fluoro$(C_2\text{-}C_5)$ alkanoyl, halo, cyano, $-OR^{36}$, $-R^{37}$, $-C(=O)R^{36}$, $-NR^{36}R^{38}$, $-C(=O)OR^{36}$, $-S(=O)_mR^{37}$ where m is 0, 1, or 2, $-S(=O)_2NR^{36}R^{38}$, $-C(=O)NR^{36}R^{38}$, $-NR^{36}S(=O)_2R^{37}$, or $-NR^{36}C(=O)R^{37}$; and

N-substituted by 0-2 of $(C_1\text{-}C_6)$ alkoxy$(C_1\text{-}C_6)$ alkyl, $R^{36}R^{38}N(C_2\text{-}C_6)$ alkyl, halo$(C_1\text{-}C_6)$ alkyl, fluoro$(C_2\text{-}C_5)$ alkanoyl, $-R^{37}$, $-C(=O)R^{36}$, $-C(=O)OR^{37}$, $-S(=O)_2R^{37}$, $-S(=O)_2NR^{36}R^{38}$, or $-C(=O)NR^{36}R^{38}$; and

(d) N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl, or morpholinyl, when B is $C_2\text{-}C_6$ alkylene,

each C-substituted by 0-2 of $(C_1\text{-}C_6)$ alkyl, phenyl, $(C_1\text{-}C_6)$ alkoxy$(C_1\text{-}C_6)$ alkyl, $R^{32}R^{34}N(C_1\text{-}C_6)$ alkyl, halo$(C_1\text{-}C_6)$ alkyl, fluoro$(C_1\text{-}C_6)$ alkoxy, $(C_2\text{-}C_5)$ alkanoyl, halo, $-OR^{32}$, cyano, $-C(=O)OR^{32}$, $(C_3\text{-}C_8)$ cycloalkyl, $-S(=O)_mR^{35}$ where m is 0, 1, or 2, $-NR^{32}R^{34}$, $-S(=O)_2NR^{32}R^{34}$, $-C(=O)NR^{32}R^{34}$, $-NR^{32}C(=O)R^{35}$, or $-NR^{32}S(=O)_2R^{35}$; and

each the piperazinyl or homopiperazinyl N-substituted by 0-2 of $(C_1\text{-}C_6)$ alkyl, phenyl, $(C_1\text{-}C_6)$ alkoxy$(C_2\text{-}C_6)$ alkyl, $R^{32}R^{34}N(C_2\text{-}C_6)$ alkyl, fluoro$(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_5)$ alkanoyl, $-C(=O)OR^{35}$, $(C_3\text{-}C_8)$ cycloalkyl, $-S(=O)_2R^{35}$, $-S(=O)_2NR^{32}R^{34}$, or $-C(=O)NR^{32}R^{34}$, wherein

R^{32} and R^{34} are each independently -H, $(C_1\text{-}C_6)$ alkyl, $(C_3\text{-}C_8)$ cycloalkyl, or phenyl, or R^{32} and R^{34} are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, homopiperidinyl, homopiperazinyl, or tetrahydroisoquinolinyl, each substituted on a ring carbon atom by 0 or 1 of $(C_1\text{-}C_6)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, phenyl, $(C_1\text{-}C_6)$ alkoxy-$(C_1\text{-}C_6)$ alkyl, $R^{54}R^{56}N$-$(C_1\text{-}C_6)$ alkyl, fluoro-$(C_1\text{-}C_6)$ alkyl, $-C(=O)NR^{54}R^{56}$, $-C(=O)OR^{54}$, or $(C_2\text{-}C_5)$ alkanoyl, further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0 or 11 of fluoro-$(C_1\text{-}C_6)$ alkoxy, halo, $-OR^{54}$, cyano, $-S(=O)_mR^{55}$, $-NR^{54}R^{56}$, $-S(=O)_2NR^{54}R^{56}$, $-NR^{54}C(=O)R^{55}$, or $-NR^{54}S(=O)_2R^{55}$, and the piperazin-1-yl and homopiperazin-1-yl are substituted on the secondary nitrogen atom by 0 or 1 of

(C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy-(C_2-C_6) alkyl, $R^{54}R^{56}N$(C_2-C_6) alkyl, fluoro(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, -C(=O)OR^{55}, (C_3-C_6) cycloalkyl, -$S(=O)_2R^{55}$, -$S(=O)_2NR^{54}R^{56}$, or -$C(=O)NR^{54}R^{56}$;

R^{35} is (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or phenyl;

R^{36} and R^{38} are each independently -H, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, phenyl, naphthyl, or HET as defined above; and

R^{37} is (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, phenyl, naphthyl, or HET as defined above;

R^{15} has the same meaning as parts (a), (b), and (c) of R^{13} defined above, including all sub-substituents thereof;

L is a bond or a linking group -C(=O)NR^{40}, where R^{40} has the same meaning as R^{11} defined above;

D is -CH_2-, -CH_2CH_2-, or -$CH_2CH_2CH_2$-, each substituted by 0 or 1 of (C_1-C_6) alkyl or (C_3-C_8) cycloalkyl;

E is -C(=O)-, -C(=S)-, -$S(=O)_2$-, or -C[=N(CN)]-;

R^{17} is R^{11} as defined above;

R^{19} is -H, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or benzyl;

R^{21} is azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, homopiperidin-3-yl, or homopiperidin-4-yl, each substituted by 0-2 of (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or benzyl; or -(C_2-C_6) alkylene-R^{42}, or -(C_1-C_6) alkylene-R^{44}; or

R^{19} and R^{21} are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl, or homopiperazinyl, each substituted on a ring nitrogen or carbon atom by 0-3 of (C_1-C_6) alkyl or (C_3-C_8) cycloalkyl, and further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0-3 of -$NR^{46}R^{48}$, where

R^{42} is $NR^{50}R^{52}$, or azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homopiperazin-1-yl, or tetrahydroisoquinolin-1-yl, each substituted on a ring carbon atom by 0 or 1 (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, phenyl, (C_1-C_6) alkoxy-(C_1-C_6) alkyl, $R^{54}R^{56}N$-(C_1-C_6) alkyl, fluoro-(C_1-C_6) alkyl, -C(=O)$NR^{54}R^{56}$, -C(=O)OR^{54}, or (C_2-C_5) alkanoyl, and further substituted on a ring carbon atom not adjacent to a ring nitrogen atom by 0 or 1 of fluoro(C_1-C_6) alkoxy, halo, -OR^{54}, cyano, -$S(=O)_mR^{55}$, -$NR^{54}R^{56}$, -$S(=O)_2NR^{54}R^{56}$, -$NR^{54}C(=O)R^{55}$, or -

$NR^{54}S(=O)_2R^{55}$, and further the piperazin-1-yl and homopiperazin-1-yl are substituted on the ring nitrogen atom not attached to the (C_2-C_6) alkylene group by 0 or 1 of (C_1-C_6) alkyl, phenyl, (C_1-C_6) alkoxy-(C_2-C_6) alkyl, $R^{54}R^{56}N$-(C_2-C_6) alkyl, fluoro-(C_1-C_6) alkyl, (C_2-C_5) alkanoyl, $-C(=O)OR^{55}$, (C_3-C_8) cycloalkyl, $-S(=O)_2R^{55}$, $-S(=O)_2NR^{54}R^{56}$, or $-C(=O)NR^{54}R^{56}$;

R^{44} is phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each substituted by 0 or 1 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, or cyano;

R^{46} and R^{48} are each independently -H or (C_1-C_6) alkyl, or, taken together with the nitrogen atom to which they are attached, represent azetidinyl, pyrrolidinyl, or piperidinyl, each substituted by 0 or 1 of (C_1-C_6) alkyl;

R^{50} is -H, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or benzyl;

R^{52} is -H, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, phenyl, benzyl, fluoro-(C_1-C_6) alkyl, $-C(=O)NR^{54}R^{56}$, $-C(=O)OR^{55}$, (C_2-C_5) alkanoyl, or $-S(=O)_2NR^{54}R^{56}$;

R^{54} and R^{56} are each independently -H, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or phenyl;

R^{55} is (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or phenyl; and

R is -H, (C_1-C_6) alkyl, or fluorenyl, where the (C_1-C_6) alkyl is substituted by 0-2 of phenyl, or naphthyl, where the phenyl or naphthyl is substituted by 0 or 2 of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, or cyano,

or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition according to one of claims 1 or 2, wherein the adenosine A_{2A} receptor agonist agent is a compound selected from the group consisting of:

9-[(2*R*,3*R*,4*S*,5*R*)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-2-phenylacetamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}benzenesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-[2-(benzylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-(cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-{[(cyclohexylmethyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-[2-[(cyclopentylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-1-propanesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-{2-(2-aminoethyl)-6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-{2-[2-(cyclohexylamino)ethyl]-6-[(2,2-diphenylethyl)amino]-2-[(isopropylamino)methyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-(2-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)benzenesulfonamide;

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-[2-(isopropylamino)ethyl]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperdinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-phenylethyl-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(4-isopropyl-1-piperdinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[3-(1-pyrrolidinyl)propyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(4-morpholinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-(2-pyridinylmethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(2-pyridinyl)ethyl]-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-*N*-[2-(dimethylamino)ethyl]-6-[(2,2-diphenylethyl)amino]- 9*H*-purine-2-carboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-(phenylethylamino)-9*H*-purin-2-yl]methyl}benzenesulfonamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(1-naphthylmethyl)amino]-9*H*-purin-2-yl}methyl)benzenesulfonamide;

2-[cyclopentyl(isopropyl)amino]-*N*-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-ethanesulfonamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[(benzylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(propylsulfonyl)amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(isopropylsulfonyl)amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(phenylsulfonyl)amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[([1,1'-biphenyl]-4-ylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(naphthylsulfonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-di-isopropylamino)ethyl]urea;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-(1-piperidinyl)ethyl]urea;

(2*S*,3*S*,4*R*,5*R*)-5-{2-{[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-{2-{[({[2-(1-piperidinyl)ethyl]amino}-carbonyl)amino]methyl}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

N-({6-{[2,2-bis(4-chlorophenyl)ethyl]amino}-9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N*-[2-(2-di-isopropylamino)ethyl]urea;

N-[2-(dicyclobutylamino)ethyl]-N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)urea;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(4-isopropyl-1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

N-{2-[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]ethyl}-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-{2-[({[2-(1-piperidinyl)ethyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-*N*-{2-[({[2-(di-isopropylamino)ethyl]amino}carbonyl)amino]ethyl}-6-[(2,2-diphenylethyl)amino] -9*H*-purine-2-carboxamide;

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[2-(4-isopropyl-1-piperidinyl)ethyl]amino}-carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide;

N-(2-{[({2-[cyclopentyl(isopropyl)amino]ethyl}amino)carbonyl]amino}ethyl)-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-9*H*-purine-2-carboxamide; and

N-(2-{[({2-[cyclohexyl(isopropyl)amino]ethyl}amino)carbonyl]amino}ethyl)-6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-9*H*-purine-2-carboxamide.

6. The pharmaceutical composition according to one of claims 1 or 2, wherein the adenosine A_{2A} receptor agonist agent is a compound disclosed generally or specifically in WO 00/23457, WO 00/77018, WO 01/27131, or WO-A-01/27130.

7. The pharmaceutical composition according to one of claims 1 or 2, wherein the adenosine A_{2A} receptor agonist agent is a compound selected from the group consisting of:

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

cis-(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)amino]-2-{[(4-isopropylcyclohexyl)amino]methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol;

trans-(2*R*,3*R*,4*S*,5*R*)-2-(6-[(2,2-diphenylethyl)amino]-2-{[(4-isopropylcyclohexyl)amino]methyl}-9*H*-purin-9-yl)-5-(methoxymethyl)tetrahydro-3,4-furandiol;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide;

(2*S*,3*S*,4*R*,5*R*)-5-(6-[(2,2-diphenylethyl)amino]-2-{[(isopropylsulfonyl)amino]methyl}-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide;

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

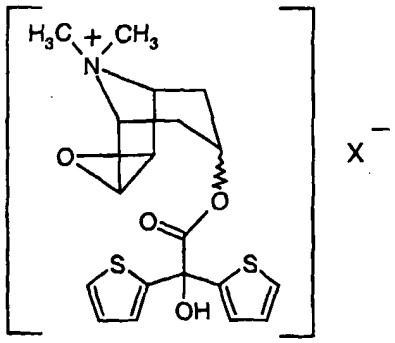
6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide;

N-({9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl}methyl)-*N'*-[2-(diisopropylamino)ethyl]urea; and

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-{2-[({[1-(2-pyridinyl)-4-piperidinyl]amino}carbonyl)amino]ethyl}-9*H*-purine-2-carboxamide,

and the pharmaceutically acceptable salts and solvates thereof.

8. The pharmaceutical composition according to claim 2, wherein the tiotropium and derivatives thereof is a compound of Formula (1.1.1):



(1.1.1)

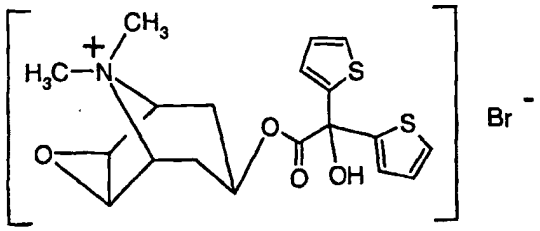
wherein X^- is a physiologically acceptable anion.

9. The pharmaceutical composition according to claim 8, wherein the physiologically acceptable anion, X^-, is selected from the group consisting of: fluoride, F^-; chloride, Cl^-; bromide, Br^-; iodide, I^-; methanesulfonate, $CH_3S(=O)_2O^-$; ethanesulfonate, $CH_3CH_2S(=O)_2O^-$; methylsulfate, $CH_3OS(=O)_2O^-$; benzene sulfonate, $C_6H_5S(=O)_2O^-$; and *p*-toluenesulfonate, 4-CH_3-$C_6H_5S(=O)_2O^-$.

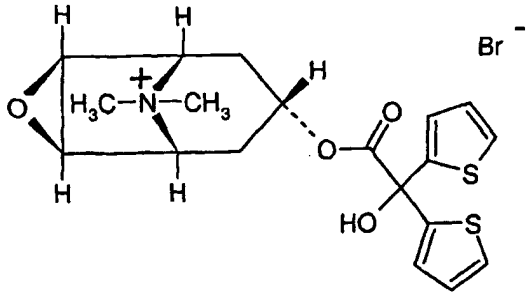
10. The pharmaceutical composition according to claim 8, wherein the physiologically acceptable anion, X^-, is bromide, Br^-.

11. The pharmaceutical composition according to claim 8, wherein the tiotropium and derivatives thereof is a 3-α compound.

12. The pharmaceutical composition according to claim 11, wherein the tiotropium and derivatives thereof is tiotropium bromide, (1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, represented by Formula (1.1.2) or Formula (1.1.3):



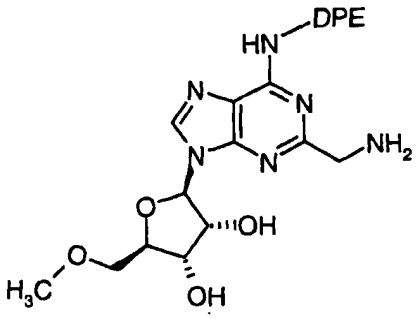
(1.1.2)



(1.1.3).

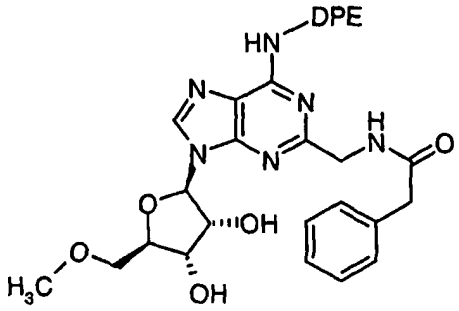
13. The pharmaceutical composition according to claim 2, wherein:

(a) the adenosine A_{2A} receptor agonist is selected from the group consisting of:



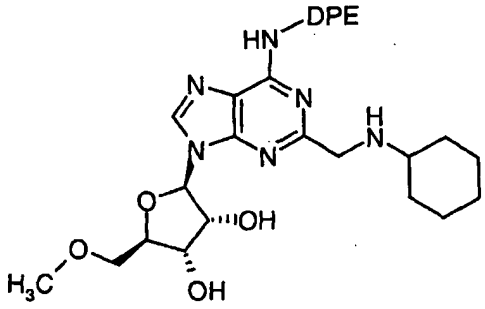
(3.0.6)

9-[(2R,3R,4S,5R)-2-{2-(aminomethyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



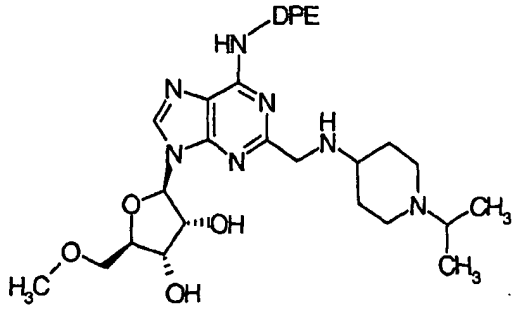
(3.0.7)

N-{[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(methoxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-2-yl]methyl}-2-phenylacetamide



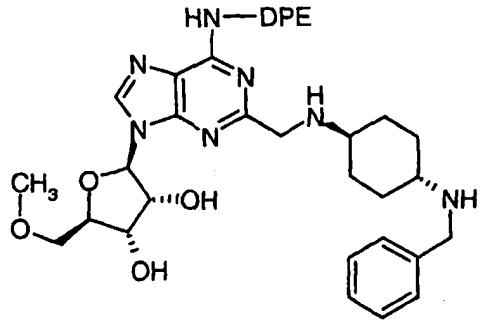
(3.0.9)

(2*R*,3*R*,4*S*,5*R*)-2-[2-(cyclohexylamino)methyl]-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl]-5-(methoxymethyl)tetrahydro-3,4-furandiol



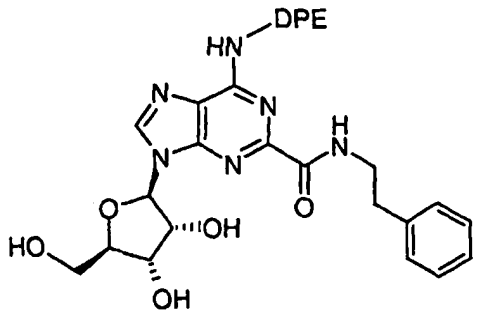
(3.0.11)

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)-amino]-2-{[(1-isopropyl-4-piperidinyl)amino]methyl}-9*H*-purin-9-yl}-5-(methoxymethyl)-tetrahydro-3,4-furandiol



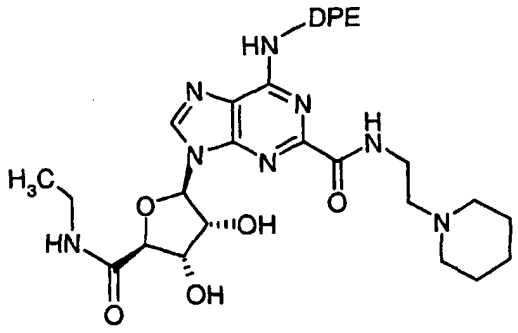
(3.0.17)

(2*R*,3*R*,4*S*,5*R*)-2-{2-({[*trans*-4-(benzylamino)cyclohexyl]amino}methyl)-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-5-(methoxymethyl)tetrahydro-3,4-furandiol



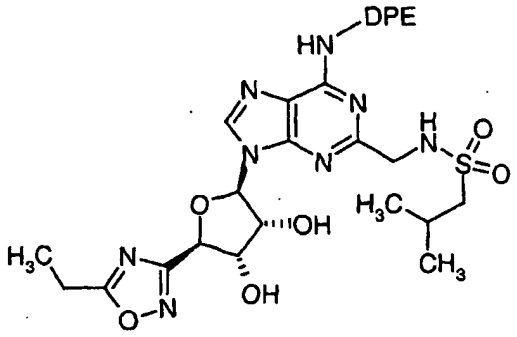
(3.0.25)

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-phenethyl-9*H*-purine-2-carboxamide



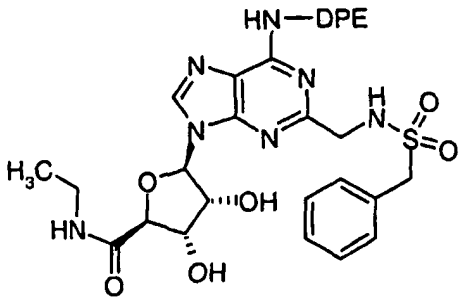
(3.0.28)

6-[(2,2-diphenylethyl)amino]-9-{(2*R*,3*R*,4*S*,5*S*)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl}-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide



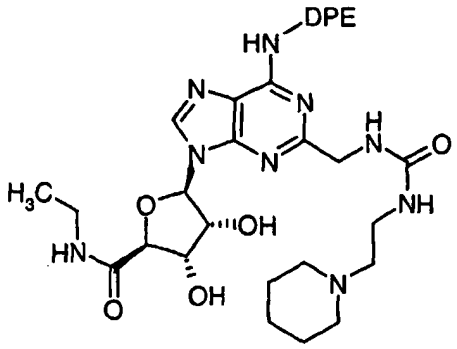
(3.0.34)

N-({6-[(2,2-diphenylethyl)amino]-9-[(2*R*,3*R*,4*S*,5*R*)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-3,4-dihydroxytetrahydro-2-furanyl]-9*H*-purin-2-yl}methyl)-2-methyl-1-propanesulfonamide



(3.0.40)

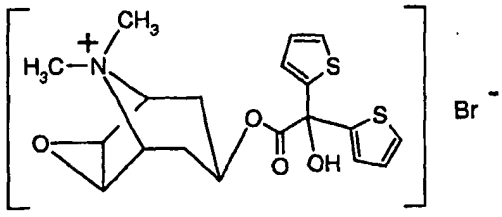
(2*S*,3*S*,4*R*,5*R*)-5-{2-{[(benzylsulfonyl)amino]methyl}-6-[(2,2-diphenylethyl)amino]-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide



(3.0.46)

(2*R*,3*R*,4*S*,5*R*)-5-(6-[(2,2-diphenylethyl)-amino]-2-{[({[2-(1-piperidinyl)ethyl]amino}-9*H*-purin-9-yl}-*N*-ethyl-3,4-dihydroxytetrahydro-2-furancarboxamide; and

(b) the anti-cholinergic agent is tiotropium bromide of Formula (1.1.2):



(1.1.2).

14. A method for the treatment of obstructive airways and other inflammatory diseases in a mammal in need of such treatment, comprising administering to the mammal by inhalation a therapeutically effective amount of a combination of therapeutic agents comprising:

(i) an adenosine A_{2A} receptor agonist; and

(ii) an anti-cholinergic agent.

15. A method for the treatment of obstructive airways and other inflammatory diseases in a mammal in need of such treatment, comprising administering to the mammal by inhalation a therapeutically effective amount of a combination of therapeutic agents comprising:

(i) an adenosine A_{2A} receptor agonist; and

(ii) an anti-cholinergic agent selected from the group consisting of tiotropium and derivatives thereof.

16. The method of treatment according to one of claims 14 or 15, wherein the obstructive airways disease is asthma, COPD, or other obstructive airways disease exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm.

17. The method of treatment according to claim 16, wherein the mammal in need of treatment is a human being.

18. The method of treatment according to claim 17, wherein the administration by inhalation comprises simultaneous or sequential delivery of the combination of therapeutic agents in the form of an aerosol or dry powder dispersion.

19. The method of treatment according to claim 18, wherein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 4.

20. The method of treatment according to claim 18, wherein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 5.

21. The method of treatment according to claim 18, wherein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 6.

22. The method of treatment according to claim 18, wherein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 7.

23. The method of treatment according to claim 18, wherein the anti-cholinergic agent is the anti-cholinergic agent specified in claim 8.

24. A pharmaceutical composition suitable for administration by inhalation, the pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier;

(b) an adenosine A_{2A} receptor agonist; and

(c) an anti-cholinergic agent,

wherein the pharmaceutical composition is therapeutically effective in the treatment of obstructive airways and other inflammatory diseases in a mammal in need of such treatment.

25. A pharmaceutical composition suitable for administration by inhalation, the pharmaceutical composition comprising:

(a) a pharmaceutically acceptable carrier;

(b) an adenosine A_{2A} receptor agonist; and

(c) an anti-cholinergic agent selected from tiotropium and derivatives thereof,

wherein the pharmaceutical composition is therapeutically effective in the treatment of obstructive airways and other inflammatory diseases in a mammal in need of such treatment.

26. The pharmaceutical composition according to one of claims 24 or 25, wherein the obstructive airways disease is asthma, COPD, or other obstructive airways disease exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm.

27. The pharmaceutical composition according to claim 26, wherein the mammal in need of treatment is a human being.

28. The pharmaceutical composition according to claim 27, wherein the administration by inhalation comprises simultaneous or sequential delivery of the pharmaceutical composition in the form of an aerosol or dry powder dispersion.

29. The pharmaceutical composition according to claim 28, wherein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 4.

30. The pharmaceutical composition according to claim 28, herein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 5.

31. The pharmaceutical composition according to claim 28, wherein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 6.

32. The pharmaceutical composition according to claim 28, herein the adenosine A_{2A} receptor agonist agent is the adenosine A_{2A} receptor agonist agent specified in claim 7.

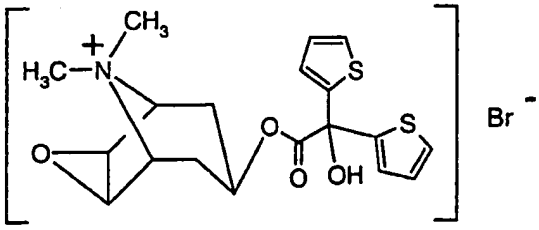
33. The pharmaceutical composition according to claim 28, wherein the anti-cholinergic agent is the anti-cholinergic agent specified in claim 8.

34. The pharmaceutical composition according to claim 33, wherein the physiologically acceptable anion, X^-, is a member selected from the group consisting of fluoride, F^-; chloride, Cl^-; bromide, Br^-; iodide, I^-; methanesulfonate, $CH_3S(=O)_2O^-$; ethanesulfonate, $CH_3CH_2S(=O)_2O^-$; methylsulfate, $CH_3OS(=O)_2O^-$; benzene sulfonate, $C_6H_5S(=O)_2O^-$; *p*-toluenesulfonate, and 4-CH_3-$C_6H_5S(=O)_2O^-$.

35. The pharmaceutical composition according to claim 34, wherein the physiologically acceptable anion, X^-, is bromide, Br^-.

36. The pharmaceutical composition according to claim 33, wherein the member of the group consisting of tiotropium and derivatives thereof is a 3-α compound.

37. The pharmaceutical composition according to claim 36, wherein the tiotropium and derivatives thereof is tiotropium bromide, (1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, represented by Formula (1.1.2):



(1.1.2).

38. A package containing a pharmaceutical composition for insertion into a device capable of simultaneous or sequential delivery of the pharmaceutical composition in the form of an aerosol or dry powder dispersion, to a mammal in need of treatment, wherein the pharmaceutical composition is the pharmaceutical composition according to one of claims 24 or 25.

39. The package according to claim 38, wherein the pharmaceutical composition is the pharmaceutical composition according to claim 27.

40. The package according to claim 38, wherein the pharmaceutical composition is the pharmaceutical composition according to claim 28.

41. The package according to claim 39, wherein the device is a metered dose inhaler, or a dry powder inhaler.

42. The package according to claim 40, wherein the device is a metered dose inhaler, or a dry powder inhaler.

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WO 02/094273 A3

(54) Title: COMBINATION OF AN ADENOSINE A2A-RECEPTOR AGONIST AND TIOTROPIUM OR A DERIVATIVE THEREOF FOR TREATING OBSTRUCTIVE AIRWAYS

(57) Abstract: A combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (i) an adenosine A_2 receptor agonist; and (ii) an anti-cholinergic agent, preferably comprising a member selected from the group consisting of tiotropium and derivatives thereof; the combination being therapeutically effective in the treatment of the diseases when administered by inhalation; as well as to a method of treating the obstructive airways and other inflammatory diseases comprising administering separately, simultaneously or sequentially to the mammal by inhalation a therapeutically effective amount of the combination of therapeutic agents; as well as to a pharmaceutical composition comprising a pharmaceutically acceptable carrier together with the combination of therapeutic agents; as well as to a product containing the compounds of the combination for separate, simultaneous or sequential administration by inhalation to a mammal for the treatment of obstructive airways and other inflammatory diseases. It is preferred that the anti-cholinergic agent component be tiotropium bromide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/05764

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52 A61K9/72 A61P11/06 A61P11/08 //(A61K31/52, 31:46)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, PASCAL, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 94368 A (STEPHENSON PETER THOMAS ;PFIZER LTD (GB); MANTELL SIMON JOHN (GB);) 13 December 2001 (2001-12-13) page 1, line 26 -page 2 ---	1-42
Y	WO 00 72799 A (LINDEN JOEL M ;UNIV VIRGINIA (US); SAREMBOCK IAN J (US); SULLIVAN) 7 December 2000 (2000-12-07) claim 1 page 13, line 14 - line 24 ---	1-42

-/--

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[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2002	20/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sindel, U

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INTERNATIONAL SEARCH REPORT

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PCT/EP 02/05764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARNES P J: "Chronic obstructive pulmonary disease: new opportunities for drug development." TRENDS IN PHARMACOLOGICAL SCIENCES. ENGLAND OCT 1998, vol. 19, no. 10, October 1998 (1998-10), pages 415-423, XP004156947 ISSN: 0165-6147 paragraph 'ANTICHOLINERGICS!	1-42

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[redacted] Application No
PCT/EP 02/05764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0194368 A	13-12-2001	AU 6053701 A	17-12-2001
		WO 0194368 A1	13-12-2001
		US 2002058641 A1	16-05-2002
WO 0072799 A	07-12-2000	AU 5294100 A	18-12-2000
		WO 0072799 A2	07-12-2000